EXHIBIT 25

Press Release

GlaxoSmithKline

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Preliminary Results Announcement for the year ended 31st December 2006

GSK delivers strong 2006 performance with full year EPS up 19% CER (16% reported)

GlaxoSmithKline plc (GSK) today announces its unaudited results for the year ended 31st December 2006. The full results are presented under 'Income Statement' on pages 7 and 8, and are summarised below.

FINANCIAL RESULTS*

	2006 £m	2005 £m	Growth CER%	Growth £%	Q4 2006 £m	Q4 2005 £m	Growth CER%	Growth £%
Turnover	**23,225**	21,660	**9**	7	**5,959**	5,907	**9**	1
Operating profit	**7,808**	6,874	**17**	14	**1,700**	1,633	**19**	4
Profit before tax	**7,799**	6,732	**19**	16	**1,710**	1,606	**22**	6
Earnings per share	**95.5p**	82.6p	**19**	16	**21.0p**	19.8p	**22**	6

SUMMARY*

- **Group turnover up 9% to £23.2 billion, driven by strong US pharmaceuticals performance, up 16%; resulting in 2006 EPS up 19% in CER terms**
- **Pharmaceuticals sales also up 9% to £20.1 billion, with strong growth from all major products:**
  - *Seretide/Advair* +11% to £3.3 billion
  - *Avandia* product group +25% to £1.6 billion
  - Vaccines +23% to £1.7 billion
  - *Lamictal* +19% to £996 million
  - *Valtrex* +24% to £845 million
  - *Coreg* +38% to £779 million
- **Consumer Healthcare sales up 6% to £3.1 billion; strong Q4 performance with sales up 9%**
- **Significant late-stage pipeline progress:**
  - 4 NCEs, 3 new vaccines and 3 in-licensed assets: *HuMax-CD20* (oncology), *gepirone ER* and XP13512 (CNS disorders) entered late-stage development in the last 12 months
  - 31 key product opportunities now in phase III/registration (13 NCEs, 6 vaccines, 12 PLEs)
- **5 major new pharmaceutical product launches expected in 2007:**
  - *Tykerb* – new oral treatment for breast cancer
  - *Cervarix* (Europe & International) – a vaccine to prevent cervical cancer (US filing by April)
  - *Allermist/Avamys* – new treatment for allergic rhinitis
  - *Coreg CR* – a once daily treatment for three cardiovascular conditions
  - *Trexima* – new treatment for migraine
- **2006 dividend of 48p (vs 44p in 2005)**
- **2007 EPS growth expected to be 8% to 10% in CER terms – driven by continued growth from key products and improvements in margin.**

Commenting on the 2006 performance and GSK's outlook, JP Garnier, Chief Executive Officer, said:
"GSK continues to make progress on all fronts. Sales growth is coming from an ever widening portfolio of fast-growing products, and sustained improvements in margin have enabled us to deliver a strong financial performance, with EPS up 19% in CER terms. We also have very healthy momentum in our pipeline, with 10 new products added to our late-stage development efforts in the last 12 months. We now have over 30 significant product opportunities in phase III development or registration, including five major new products planned for launch this year. For all these reasons, we look to the future with confidence."

* The Group's practice is to discuss its results in terms of constant exchange rate (CER) growth. All commentaries compare 2006 results with 2005 in CER terms unless otherwise stated. See 'Accounting Presentation and Policies' on page 22.

PHARMACEUTICAL UPDATE

Total pharmaceutical turnover grew 9% to £20.1 billion

A strong sales performance in the **USA**, up 16% to £10.4 billion helped drive total pharmaceutical turnover growth of 9% in 2006. Sales in **Europe** grew 1%, to over £5.5 billion, with strong sales from *Seretide*, *Avandia/Avandamet* and vaccines offsetting the impact of generic competition to *Lamictal*, *Imigran* and *Zofran*, and continued price cuts. **International** region sales grew 6% to £4.2 billion, with sales in Japan up 8% to £860 million.

***Seretide/Advair* sales over £3.3 billion; TORCH data publication in H1 2007**

Total sales of ***Seretide/Advair***, for asthma and COPD, rose 11% to £3.3 billion. In the USA, sales grew 13% to £1.9 billion. In Europe, sales grew 10% to £1.1 billion and in International markets, sales grew 9% to over £300 million. GSK expects the positive results from TORCH, a COPD mortality study recently filed with regulators, to be published in a leading medical journal during the first half of 2007.

***Avandia* product group sales over £1.6 billion with strong growth across all regions**

Sales of ***Avandia*** products, for the treatment of type 2 diabetes, grew 24% to £1.2 billion in the USA. In Europe, sales grew 40% to £217 million driven by the increasing use of ***Avandamet***. Sales in International markets rose 19% to £234 million.

In December, GSK presented data from the landmark ADOPT study, which demonstrated that *Avandia* is more effective than metformin, or a sulphonylurea, in long-term blood sugar control in type 2 diabetes. These data are in addition to those recently presented from the DREAM study, which showed that *Avandia* can reduce the risk of progression to type 2 diabetes. Data from both these studies are expected to be filed with regulatory agencies during the first half of 2007.

Strong 2006 for vaccines with new products driving sales up 23% to £1.7 billion

Overall vaccine sales increased 23% to £1.7 billion, with good performances from all regions: US sales rose 40% to £465 million; European sales grew 20% to £709 million and sales in International were up 13% to £518 million. Key contributors were: ***Infanrix/Pediarix***, GSK's combination vaccines for children, with sales up 29% to £511 million; and sales of hepatitis vaccines, which grew 9% to £479 million, benefiting from a strong US performance of ***Havrix***, following approval last year for broader paediatric use.

Sales of new vaccines also helped drive overall sales growth. Total sales of ***Rotarix***, for rotavirus, ***Boostrix***, for prevention of diphtheria, tetanus and whooping cough, and influenza vaccines, ***Fluarix/FluLaval***, reached £274 million, up 91%.

***Lamictal, Valtrex,* and *Coreg* – sales grew 26% to over £2.6 billion**

Sales of ***Lamictal***, for the treatment of epilepsy and bipolar disorder, grew 19% to just under £1 billion, benefiting from its new indication to treat one of the most serious forms of epilepsy – primary generalised tonic-clonic seizures. *Lamictal* is also the only medicine with long-term clinical data that demonstrates that it can delay the onset of depressive episodes of bipolar disorder. In November, GSK submitted ***Lamictal XR***, a new once daily treatment, with the FDA for treatment of epilepsy. The company intends to present data on *Lamictal XR* at the American Academy of Neurology meeting in April.

Sales of ***Valtrex***, for herpes, rose 24% to £845 million, with US sales up 30% to £600 million. Sales of ***Coreg***, for heart disease, grew strongly, up 38% to £779 million.

High potential products - *Avodart, Requip* and *Boniva* deliver combined sales of £579 million

Sales of ***Requip,*** for Parkinson's disease/Restless Legs Syndrome (RLS), grew 74% to £268 million and, in December, the FDA accepted GSK's file for approval of ***Requip 14hr***. ***Avodart*** for benign prostatic hyperplasia (enlarged prostate), continued to perform strongly with sales up 69% to £216 million for the year. GSK's share of the co-promotion income for ***Boniva/Bonviva***, the only once-monthly medicine for post-menopausal osteoporosis, was £95 million.

Other products

Total sales of HIV products were £1.5 billion, down 1%. Competition to older products, ***Combivir*** (-9% to £528 million) and ***Epivir*** (-21% to £202 million), was partially offset by strong sales growth of new products ***Epzicom/Kivexa*** (>100% to £241 million) and ***Lexiva*** (+18% to £131 million).

Sales of ***Flonase*** fell 52% to £311 million, reflecting generic competition in the USA, which began in the first quarter of 2006.

Fourth quarter pharmaceutical sales up 8% to £5.1 billion

A strong fourth quarter performance was driven by US sales, up 15% to £2.6 billion, despite the introduction of generic competition to ***Wellbutrin XL*** 300mg tablet (approximately 60% of *Wellbutrin* sales) and ***Zofran***. Fourth quarter sales of *Wellbutrin XL* were up 9% to £187 million, compared with full year sales growth of 25% to £798 million. Fourth quarter sales of *Zofran* declined 19% to £165 million, compared with full year growth of 3% to £847 million. In Europe, total pharmaceutical sales grew 1% to over £1.4 billion and in International markets rose 3% to £1.1 billion.

PIPELINE UPDATE

GSK expects to launch 5 major new products in 2007:

***Tykerb* – US launch expected in H1 2007**

In December, landmark clinical trial data for *Tykerb* were published in the New England Journal of Medicine. Data from the study reported that *Tykerb* in combination with Xeloda, significantly improved the time to disease progression for patients with HER2 (ErbB2+) advanced breast cancer whose disease had progressed on Herceptin. In addition, the study authors concluded that further investigation into earlier use of *Tykerb* in the treatment of HER2 positive breast cancer is warranted.

Subject to regulatory approval, GSK plans to launch *Tykerb* in the USA during the first half of 2007 and in Europe in the second half of the year. Meanwhile, clinical development of *Tykerb* continues with seven phase III trials ongoing to assess the use of *Tykerb* in treatment of adjuvant and first-line metastatic breast cancer.

***Cervarix* – European/International launches expected in H2 2007; US filing by April**

GSK expects to launch *Cervarix*, a new vaccine to prevent cervical cancer, in European and International markets in the second half of 2007. The company remains on track to file for regulatory approval in the USA by April.

Earlier this year, GSK announced the initiation of the first head-to-head trial of *Cervarix* versus Gardasil, to compare the immune responses to HPV types 16 and 18 in US women 18 to 45 years old. Initial study results are anticipated in 2008.

***Allermist/Avamys* – US launch H1 2007; new phase III data to be presented at AAAAI**

Allermist/Avamys, a new intranasal steroid to treat the symptoms of seasonal allergic rhinitis and perennial allergic rhinitis, is expected to be launched in the first half of 2007. GSK will present new phase III data on the product at the annual meeting of the American Academy of Allergy, Asthma & Immunology (AAAAI) beginning on 23rd February.

***Coreg CR* – Launch in Q1 2007; new opportunity to simplify treatment**

Coreg CR is a new once-daily, long acting treatment for three cardiovascular conditions: hypertension, post-myocardial infarction left ventricular dysfunction and mild to severe heart failure. It represents a significant new opportunity to help simplify treatment for those patients taking multiple medications for heart conditions, in particular hypertension. The company intends to launch *Coreg CR* in the first quarter of 2007.

***Trexima* - New data submitted to FDA; launch expected H2 2007**

A full response to the FDA's recent request for additional information has now been submitted to the agency. Subject to regulatory approval, GSK expects to launch *Trexima*, for the treatment of migraine, in the second half of 2007.

Other important launches/filings

GSK also expects to launch several other important products during the year including, ***Arixtra*** to treat acute coronary syndromes (ACS); ***Altabax/Altargo***, for skin infections, and ***Entereg*** for the management of post-operative ileus.

The company plans to file several new products for approval with regulatory authorities in 2007, including two major vaccine opportunities: US filing of ***Rotarix***; and European filing of ***Synflorix*** (formerly *Streptorix*), a vaccine to prevent pneumococcal disease.

GSK also continues to progress development of vaccines for use before, and in the event of, a 'flu pandemic; and in January, submitted its **H5N1 vaccine** to European regulators for approval for pre-pandemic use.

Significant late-stage pipeline progress:

The company now has 31 major product opportunities in phase III development or registration, comprising 13 NCEs, 6 new vaccines and 12 product line extensions.

Major NCEs & vaccines (* entered late-stage in the last 12 months)

Phase III

- **ambrisentan** (pulmonary arterial hypertension)
- **belimumab*** (lupus)
- **casopitant*** (CINV and PONV)
- **pazopanib*** (renal cell cancer)
- **mepolizumab** (hypereosinophilic syndrome)
- ***Promacta*** * (ITP)
- **New generation 'flu vaccine***
- ***Globorix*** (Hep B, DTP, Hib and meningitis A+C)
- **meningitis (Hib-MenCY-TT) vaccine***
- ***Synflorix*** (pneumococcal disease)

Filed

- ***Allermist/Avamys*** (allergic rhinitis)
- ***Altabax/Altargo*** (skin infections)
- ***Entereg*** (POI)
- ***Tykerb*** (breast cancer)
- ***Cervarix*** (cervical cancer)
- **H5N1 pandemic vaccine***

New in-licensed assets

- ***HuMax-CD20****, a high affinity (fully human) monoclonal antibody in late-stage development for chronic lymphocytic leukaemia and follicular non-Hodgkin's lymphoma; and in phase II development for rheumatoid arthritis.

- ***Gepirone ER****, a 5HT1a agonist currently in pre-registration for the treatment of major depressive disorder (MDD). If approved, *gepirone ER* would be a first-in-class treatment for MDD, with a potentially better tolerability profile compared to current anti-depressant therapy.

- **XP13512***, a gabapentin prodrug, in phase III development for restless legs syndrome and phase II for treatment of neuropathic pain. In addition to a convenient dosing regimen, XP13512 could provide a new treatment option to patients for whom current therapy (dopaminergics) is not appropriate.

CONSUMER HEALTHCARE UPDATE

Sales up 6% to over £3.1 billion; portfolio to be enhanced with 10 product launches in 2007

Consumer Healthcare sales grew 6% to £3.1 billion, with sales in International (+10%) and Europe (+7%), performing well. Total sales in the USA were flat, with an improved performance seen in the fourth quarter, with sales up 7% to over £200 million.

- **Nutritional healthcare** products sales grew 7% to £658 million. ***Lucozade***, grew 14% to £301 million, and ***Horlicks***, grew 6% to £156 million. ***Ribena*** sales were down 1% to £169 million.
- **Oral care** sales grew 6% to £993 million. ***Sensodyne*** grew strongly, up 19% for the year to £257 million. Sales of ***Aquafresh*** were down 3% to £283 million.
- **Over-the-counter** medicine sales grew 5% to £1.5 billion with ***Panadol*** and Smoking Control performing well.

GSK's consumer brand portfolio will be strengthened further in 2007, with the launch of 10 products, including ***alli***, a new treatment for weight-loss in the USA. In addition, GSK has added two more brands – ***Breathe Right*** nasal strips and ***FiberChoice*** dietary fibre supplements – to its portfolio following the acquisition of CNS, Inc. which was completed in December 2006.

FINANCIAL REVIEW

These results have been prepared under International Financial Reporting Standards as adopted for use in the European Union (see 'Accounting Presentation and Policies' on page 22).

Operating profit and earnings per share – full year

Operating profit of £7,808 million for the year increased by 17% compared with 2005, and was above turnover growth of 9%, reflecting an improved cost of sales margin (despite higher restructuring costs), flat SG&A costs (including lower legal and restructuring charges), partially offset by an increase in R&D expenditure and lower other operating income. Excluding restructuring, R&D expenditure grew in line with turnover growth.

Consumer Healthcare operating profit was down 3%, compared with 2005, as a result of lower profit on product disposals. Excluding profit on disposals, Consumer Healthcare operating profit grew 4%.

In the year, gains from asset disposals were £169 million (£290 million in 2005), costs for legal matters were £333 million (£430 million in 2005), the fair value movements on the Quest collar and Theravance options resulted in income of £29 million (£19 million income in 2005) and charges related to restructuring programmes were £205 million (£141 million in 2005). The total operating profit impact of these items was a £340 million charge in 2006, compared with a £262 million charge in 2005.

Profit after taxation grew by 17%, which was level with the growth in operating profit, and reflected lower net interest costs, offset by a higher tax rate for the year.

EPS of 95.5 pence increased 19% in CER terms (16% in sterling terms) compared with 2005. The adverse currency impact of 3% on EPS reflected the strength of sterling against other major currencies.

Operating profit and earnings per share – Q4

Operating profit of £1,700 million for the quarter increased by 19% compared with Q4 last year, and was above turnover growth of 9%, primarily due to flat SG&A (including lower legal costs), lower growth in R&D and higher other operating income partly offset by a higher cost of sales margin. The cost of sales margin was primarily impacted by higher restructuring costs, asset impairments and currency, partly offset by favourable pricing.

In the quarter, gains from asset disposals were £3 million (£12 million in 2005), costs for legal matters were £81 million (£132 million in 2005), the fair value movements on the Quest collar and Theravance options resulted in income of £46 million (£4 million income in Q4 2005) and charges related to restructuring programmes were £132 million (£59 million in 2005). The total operating profit impact of these items was a £164 million charge in 2006, compared with a £175 million charge in Q4 2005.

Profit after taxation grew by 20% which was marginally higher than the growth in operating profit and reflected lower net interest costs compared with Q4 2005, largely offset by a higher tax rate.

EPS of 21.0 pence increased 22% in CER terms (6% in sterling terms) compared with Q4 2005. The adverse currency impact of 16% on EPS reflected the strength of sterling against the other major currencies.

Currencies

The 2006 results are based on average exchange rates, principally £1/$1.85, £1/Euro 1.47 and £1/Yen 215. The period-end exchange rates were £1/$1.96, £1/Euro 1.48 and £1/Yen 233. Average exchange rates for Q4 2006 were £1/$1.94, £1/Euro 1.50 and £1/Yen 227. If the US dollar and Euro exchange rates were to hold at the Q4 average level for 2007, the adverse currency impact on EPS growth for the full-year would be around 4%.

Dividend

The Board has declared a fourth interim dividend of 14 pence per share resulting in a dividend for the year of 48 pence, a four pence increase over the dividend of 44 pence per share for 2005. The equivalent interim dividend receivable by ADR holders is 55.1628 cents per ADS based on an exchange rate of £1/$1.9701. The dividend will have an ex-dividend date of 14th February 2007, a record date of 16th February 2007 and will be paid on 12th April 2007.

2007 earnings guidance

GSK expects 2007 EPS growth to be 8% to 10% in CER terms.

Share buy-back programme

GSK repurchased £1,348 million of shares in 2006, to be held as Treasury shares. The company completed its second £4 billion share repurchase programme in September, and in October commenced a new share buy-back programme totalling £6 billion. This programme is expected to be completed over a three year period including £2 billion in 2007. The exact amount and timing of future purchases, and the extent to which repurchased shares will be held as Treasury shares rather than being cancelled, will be determined by the company and is dependent on market conditions and other factors.

GlaxoSmithKline – one of the world's leading research-based pharmaceutical and healthcare companies – is committed to improving the quality of human life by enabling people to do more, feel better and live longer. For company information including a copy of this announcement and details of the company's updated product development pipeline, visit GSK at www.gsk.com.

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Cautionary statement regarding forward-looking statements
Under the safe harbor provisions of the US Private Securities Litigation Reform Act of 1995, the company cautions investors that any forward-looking statements or projections made by the company, including those made in this Announcement, are subject to risks and uncertainties that may cause actual results to differ materially from those projected. Factors that may affect the Group's operations are described under 'Risk Factors' in the 'Operating and Financial Review and Prospects' in the company's Annual Report 2005.

INCOME STATEMENT
Year ended 31st December 2006

	2006 £m	Growth CER%	2005 £m
Turnover:			
Pharmaceuticals	20,078	9	18,661
Consumer Healthcare	3,147	6	2,999
TURNOVER	23,225	9	21,660
Cost of sales	(5,010)	6	(4,764)
Gross profit	18,215	9	16,896
Selling, general and administration	(7,257)	-	(7,250)
Research and development	(3,457)	11	(3,136)
Other operating income	307		364
Operating profit:			
Pharmaceuticals	7,125	19	6,159
Consumer Healthcare	683	(3)	715
OPERATING PROFIT	7,808	17	6,874
Finance income	287		257
Finance expense	(352)		(451)
Share of after tax profits of associates and joint ventures	56		52
PROFIT BEFORE TAXATION	7,799	19	6,732
Taxation (includes overseas tax of £1,912 million (2005: £1,826 million))	(2,301)		(1,916)
Tax rate %	*29.5%*		*28.5%*
PROFIT AFTER TAXATION FOR THE YEAR	5,498	17	4,816
Profit attributable to minority interests	109		127
Profit attributable to shareholders	5,389		4,689
	5,498		4,816
EARNINGS PER SHARE	95.5p	19	82.6p
Diluted earnings per share	94.5p		82.0p

A fourth interim dividend of 14 pence per share has been declared, making a total of 48 pence per share for the year (2005: 44 pence per share). The total expected to be absorbed by these dividends is approximately £2,695 million (2005: £2,494 million). See 'Dividends' on page 14.

INCOME STATEMENT
Three months ended 31st December 2006

	Q4 2006 £m	Growth CER%	Q4 2005 £m
Turnover:			
Pharmaceuticals	5,136	8	5,108
Consumer Healthcare	823	9	799
TURNOVER	5,959	9	5,907
Cost of sales	(1,445)	15	(1,298)
Gross profit	4,514	7	4,609
Selling, general and administration	(1,934)	-	(2,040)
Research and development	(980)	6	(968)
Other operating income	100		32
Operating profit:			
Pharmaceuticals	1,501	21	1,440
Consumer Healthcare	199	8	193
OPERATING PROFIT	1,700	19	1,633
Finance income	83		85
Finance expense	(86)		(125)
Share of after tax profits of associates and joint ventures	13		13
PROFIT BEFORE TAXATION	1,710	22	1,606
Taxation	(505)		(455)
Tax rate %	*29.5%*		*28.3%*
PROFIT AFTER TAXATION FOR THE PERIOD	1,205	20	1,151
Profit attributable to minority interests	24		29
Profit attributable to shareholders	1,181		1,122
	1,205		1,151
EARNINGS PER SHARE	21.0p	22	19.8p
Diluted earnings per share	20.8p		19.6p

PHARMACEUTICAL TURNOVER
Year ended 31st December 2006

	Total		USA		Europe		International	
	£m	CER%	£m	CER%	£m	CER%	£m	CER%
RESPIRATORY	**4,995**	**-**	**2,461**	**(3)**	**1,697**	**3**	**837**	**4**
Seretide/Advair	3,313	11	1,870	13	1,133	10	310	9
Flixotide/Flovent	659	5	298	18	173	(8)	188	2
Serevent	291	(10)	86	(16)	140	(13)	65	5
Flixonase/Flonase	311	(52)	184	(63)	51	(15)	76	(14)
CENTRAL NERVOUS SYSTEM	**3,642**	**15**	**2,588**	**28**	**595**	**(15)**	**459**	**2**
Seroxat/Paxil	620	4	175	35	149	(20)	296	5
Paxil IR	448	(5)	19	11	149	(20)	280	4
Paxil CR	172	37	156	38	-	-	16	25
Wellbutrin	900	24	882	24	2	-	16	7
Wellbutrin IR, SR	102	12	89	14	2	-	11	-
Wellbutrin XL	798	25	793	25	-	-	5	25
Imigran/Imitrex	711	3	551	11	118	(18)	42	(12)
Lamictal	996	19	765	37	175	(22)	56	2
Requip	268	74	176	>100	81	21	11	25
ANTI-VIRALS	**2,827**	**10**	**1,354**	**7**	**855**	**11**	**618**	**16**
HIV	**1,515**	**(1)**	**700**	**(7)**	**621**	**3**	**194**	**8**
Combivir	528	(9)	238	(14)	217	(4)	73	-
Trizivir	268	(11)	141	(13)	113	(7)	14	(7)
Epivir	202	(21)	69	(25)	90	(26)	43	(2)
Ziagen	117	(13)	48	(11)	41	(24)	28	4
Agenerase, Lexiva	131	18	74	7	48	40	9	14
Epzicom/Kivexa	241	>100	125	49	97	>100	19	>100
Herpes	**965**	**19**	**610**	**30**	**144**	**4**	**211**	**3**
Valtrex	845	24	600	30	109	12	136	10
Zovirax	120	(6)	10	67	35	(15)	75	(7)
Zeffix	162	12	13	8	23	10	126	13
Relenza	91	>100	-	-	62	>100	29	>100
METABOLIC	**1,875**	**27**	**1,277**	**30**	**252**	**33**	**346**	**12**
Avandia	1,399	23	1,068	26	125	13	206	13
Avandamet	204	17	86	(22)	92	>100	26	41
Avandaryl	42	-	40	-	-	-	2	-
Bonviva/Boniva	95	>100	83	>100	12	>100	-	-
VACCINES	**1,692**	**23**	**465**	**40**	**709**	**20**	**518**	**13**
Hepatitis	479	9	161	21	227	2	91	8
Influenza	170	60	91	>100	36	-	43	27
Infanrix/Pediarix	511	29	172	20	281	40	58	12
Boostrix	60	>100	41	>100	15	88	4	67
CARDIOVASCULAR AND UROGENITAL	**1,636**	**24**	**1,072**	**42**	**395**	**(4)**	**169**	**13**
Coreg	779	38	773	38	-	-	6	20
Levitra	43	8	41	20	1	(75)	1	(100)
Avodart	216	69	131	>100	69	25	16	67
Arixtra	58	>100	32	>100	23	>100	3	>100
Fraxiparine	209	(1)	-	-	179	-	30	(6)
ANTI-BACTERIALS	**1,369**	**(9)**	**217**	**(15)**	**628**	**(12)**	**524**	**(2)**
Augmentin	570	(14)	94	(31)	268	(15)	208	-
Zinnat/Ceftin	164	(16)	12	20	82	(27)	70	(5)
ONCOLOGY AND EMESIS	**1,069**	**7**	**836**	**12**	**153**	**(7)**	**80**	**(11)**
Zofran	847	3	679	8	107	(14)	61	(16)
Hycamtin	113	15	72	11	34	26	7	17
OTHER	**973**	**(5)**	**83**	**19**	**263**	**(19)**	**627**	**(1)**
Zantac	232	(2)	72	28	52	(19)	108	(7)
	20,078	**9**	**10,353**	**16**	**5,547**	**1**	**4,178**	**8**

Pharmaceutical turnover includes co-promotion income.

PHARMACEUTICAL TURNOVER
Three months ended 31st December 2006

	Total		USA		Europe		International	
	£m	CER%	£m	CER%	£m	CER%	£m	CER%
RESPIRATORY	**1,269**	**(3)**	**616**	**(7)**	**433**	**1**	**220**	**-**
Seretide/Advair	862	9	493	11	293	8	76	1
Flixotide/Flovent	172	7	79	22	42	(12)	51	4
Serevent	74	(9)	22	(17)	33	(13)	19	11
Flixonase/Flonase	48	(69)	17	(85)	11	(15)	20	(8)
CENTRAL NERVOUS SYSTEM	**915**	**13**	**660**	**25**	**137**	**(17)**	**118**	**(3)**
Seroxat/Paxil	163	11	49	72	35	(10)	79	(1)
Paxil IR	113	-	3	-	35	(10)	75	-
Paxil CR	50	50	46	59	-	-	4	(25)
Wellbutrin	212	9	208	10	-	-	4	(25)
Wellbutrin IR, SR	25	13	22	25	-	-	3	(33)
Wellbutrin XL	187	9	186	9	-	-	1	-
Imigran/Imitrex	174	2	138	12	25	(34)	11	-
Lamictal	257	23	204	39	39	(22)	14	-
Requip	76	62	52	97	21	16	3	-
ANTI-VIRALS	**706**	**9**	**333**	**8**	**210**	**11**	**163**	**11**
HIV	**360**	**(5)**	**168**	**(7)**	**146**	**(3)**	**46**	**2**
Combivir	119	(14)	56	(15)	48	(9)	15	(20)
Trizivir	61	(14)	32	(16)	25	(13)	4	-
Epivir	43	(24)	15	(23)	18	(34)	10	-
Ziagen	28	(12)	12	(7)	10	(9)	6	(22)
Agenerase, Lexiva	34	12	19	5	12	18	3	50
Epzicom/Kivexa	69	66	33	29	29	100	7	>100
Herpes	**242**	**18**	**154**	**30**	**36**	**9**	**52**	**(5)**
Valtrex	212	23	150	28	27	17	35	6
Zovirax	30	(9)	4	>100	9	(10)	17	(22)
Zeffix	42	5	3	33	6	-	33	3
Relenza	37	>100	-	-	22	>100	15	>100
METABOLIC	**474**	**34**	**321**	**45**	**69**	**27**	**84**	**7**
Avandia	324	25	246	32	30	7	48	4
Avandamet	68	54	32	40	27	75	9	60
Avandaryl	14	-	14	-	-	-	-	-
Bonviva/Boniva	34	>100	29	>100	5	-	-	-
VACCINES	**527**	**31**	**162**	**84**	**200**	**20**	**165**	**10**
Hepatitis	128	19	43	38	60	11	25	8
Influenza	107	>100	59	>100	23	(12)	25	>100
Infanrix/Pediarix	136	29	47	37	72	36	17	(11)
Boostrix	18	73	13	63	5	67	-	-
CARDIOVASCULAR AND UROGENITAL	**421**	**25**	**281**	**44**	**101**	**(1)**	**39**	**(9)**
Coreg	199	39	198	39	-	-	1	-
Levitra	12	30	12	44	-	-	-	-
Avodart	61	67	36	95	19	27	6	67
Arixtra	21	>100	12	>100	7	>100	2	-
Fraxiparine	53	(2)	-	-	44	(4)	9	11
ANTI-BACTERIALS	**354**	**(8)**	**57**	**(15)**	**164**	**(9)**	**133**	**(3)**
Augmentin	145	(11)	25	(20)	67	(15)	53	2
Zinnat/Ceftin	42	(19)	3	-	22	(24)	17	(14)
ONCOLOGY AND EMESIS	**213**	**(11)**	**162**	**(10)**	**33**	**(15)**	**18**	**(20)**
Zofran	165	(19)	130	(16)	21	(30)	14	(25)
Hycamtin	28	20	18	18	8	50	2	(50)
OTHER	**257**	**2**	**18**	**5**	**60**	**(7)**	**159**	**6**
Zantac	55	(5)	16	12	13	(24)	26	(3)
	5,136	8	2,610	15	1,427	1	1,099	3

Pharmaceutical turnover includes co-promotion income.

CONSUMER HEALTHCARE TURNOVER
Year ended 31st December 2006

	2006 £m	Growth CER%
Over-the-counter medicines	**1,496**	**5**
Analgesics	380	7
Dermatological	165	4
Gastrointestinal	252	2
Respiratory tract	172	12
Smoking control	353	7
Natural wellness support	132	-
Oral care	**993**	**6**
Nutritional healthcare	**658**	7
Total	**3,147**	**6**

CONSUMER HEALTHCARE TURNOVER
Three months ended 31st December 2006

	Q4 2006 £m	Growth CER%
Over-the-counter medicines	**409**	**9**
Analgesics	95	9
Dermatological	43	15
Gastrointestinal	63	3
Respiratory tract	54	8
Smoking control	103	18
Natural wellness support	38	11
Oral care	**258**	**10**
Nutritional healthcare	**156**	**5**
Total	**823**	**9**

FINANCIAL REVIEW – INCOME STATEMENT

Operating profit

	2006		2005		Growth	
	£m	% of turnover	£m	% of turnover	CER%	£%
Turnover	**23,225**	**100.0**	21,660	100.0	9	7
Cost of sales	**(5,010)**	**(21.6)**	(4,764)	(22.0)	6	5
Selling, general and administration	**(7,257)**	**(31.2)**	(7,250)	(33.5)	-	-
Research and development	**(3,457)**	**(14.9)**	(3,136)	(14.5)	11	10
Other operating income	**307**	**1.3**	364	1.7		
Operating profit	**7,808**	**33.6**	6,874	31.7	17	14

Overall, the operating margin increased 1.9 percentage points as sterling operating profit increased 14% on a sterling turnover growth of 7% reflecting lower growth in cost of sales and flat SG&A costs, partially offset by an increase in R&D expenditure and lower other operating income.

Cost of sales declined as a percentage of turnover by 0.4 percentage points, reflecting favourable price and regional mix.

SG&A costs were level with 2005 benefiting from lower legal charges and restructuring costs. Excluding these items SG&A costs grew 3% reflecting the continuing benefits of cost saving programmes.

R&D expenditure increased 11% partly as a result of higher charges related to restructuring programmes. Excluding restructuring costs R&D grew 8%. Pharmaceuticals R&D expenditure excluding restructuring costs represented 16.2% (2005: 16.2%) of pharmaceutical turnover.

Other operating income includes royalty income, equity investment disposals and impairments, product disposals and fair value adjustments to the Quest collar and Theravance options. Other operating income was £307 million in 2006 compared with £364 million in 2005. The decrease is primarily due to lower product and asset disposal profits partially offset by the favourable fair value movement to the Quest collar and Theravance options.

Taxation

The charge for taxation on profit amounting to £2,301 million, represents an effective tax rate of 29.5%, (2005 - 28.5%). The Group balance sheet at 31st December 2006 included a tax payable liability of £621 million and a tax recoverable asset of £186 million.

As reported last year, GSK's largest unresolved tax issues were with the US Internal Revenue Service (IRS) and UK HM Revenue and Customs (HMRC) in respect of transfer prices related to the Glaxo heritage products.

On 11th September 2006, GSK and the IRS agreed to a resolution of their dispute. Under the agreement, GSK has made gross payments to the IRS of approximately $3.3 billion. The final net cash cost to the Group is approximately $3.1 billion, which covers federal, state and local taxes, interest and the benefit of tax relief on the payments made. The settlement resolved all the transfer pricing issues in dispute for the period 1989 – 2000, which were due to go to trial in February 2007, and also covers the subsequent years 2001 – 2005. GSK had previously made provision for the dispute and this settlement did not have any significant impact on the company's reported earnings or tax rate for the year.

GSK continues to be in dispute with HMRC primarily in respect of transfer pricing and Controlled Foreign Companies legislation matters for the years 1994 to date and the parties are now preparing for litigation. HMRC has not formally quantified its claims in respect of these matters but there continues to be a wide difference between the Group and HMRC positions on these matters.

GSK has open issues in Japan and Canada, which were the subject of court proceedings in 2006. In Japan the tax authorities are claiming approximately Yen 39 billion (£169 million) in respect of transactions in 1998. GSK has paid the tax claimed, as required by law, and applied for a refund. A court decision is expected in late March 2007. A court decision in the Group's dispute with the Canadian Revenue Authority over the pricing of *Zantac* in the years 1989 – 1993 is expected in the first half of 2007.

GSK uses the best advice in determining its transfer pricing methodology and in seeking to manage transfer pricing issues to a satisfactory conclusion and, on the basis of external professional advice, continues to believe that it has made adequate provision for the liabilities likely to arise from open assessments. The ultimate liability for such matters may vary from the amounts provided and is dependent upon the outcome of litigation proceedings and negotiations with the relevant tax authorities.

Weighted average number of shares

	2006 millions	2005 millions
Weighted average number of shares – basic	**5,643**	5,674
Dilutive effect of share options and share awards	**57**	46
Weighted average number of shares – diluted	**5,700**	5,720

	Q4 2006 millions	Q4 2005 millions
Weighted average number of shares – basic	**5,618**	5,657
Dilutive effect of share options and share awards	**51**	53
Weighted average number of shares – diluted	**5,669**	5,710

The number of shares in issue, excluding those held by the ESOP Trusts and those held as Treasury shares at 31st December 2006, was 5,603 million (31st December 2005: 5,653 million).

Dividends

	Paid/ payable	Pence per share	£m
2006			
First interim	6th July 2006	11	619
Second interim	5th October 2006	11	620
Third interim	4th January 2007	12	671
Fourth interim	12th April 2007	14	785
		48	2,695
2005			
First interim	7th July 2005	10	568
Second interim	6th October 2005	10	567
Third interim	5th January 2006	10	568
Fourth interim	6th April 2006	14	791
		44	2,494

The liability for an interim dividend is only recognised when it is paid, which is usually after the accounting period to which it relates. The 2006 financial statements recognise the dividends paid in 2006, namely the third and fourth interim dividends for 2005 and the first and second interim dividends for 2006, which total £2,598 million (2005: £2,390 million).

STATEMENT OF RECOGNISED INCOME AND EXPENSE

	2006 £m	2005 £m
Exchange movements on overseas net assets	(390)	203
Tax on exchange movements	(78)	99
Fair value movements on available-for-sale investments	84	(1)
Deferred tax on fair value movements on available-for-sale investments	(15)	(10)
Exchange movements on goodwill in reserves	31	9
Actuarial gains/(losses) on defined benefit plans	429	(794)
Deferred tax on actuarial movements in defined benefit plans	(161)	257
Fair value movements on cash flow hedges	(5)	(4)
Deferred tax on fair value movements on cash flow hedges	2	1
Net losses recognised directly in equity	(103)	(240)
Profit for the year	5,498	4,816
Total recognised income and expense for the year	5,395	4,576
Total recognised income and expense for the year attributable to:		
Shareholders	5,307	4,423
Minority interests	88	153
	5,395	4,576

BALANCE SHEET

	31st December 2006 £m	31st December 2005 £m
ASSETS		
Non-current assets		
Property, plant and equipment	6,930	6,652
Goodwill	758	696
Other intangible assets	3,293	3,383
Investments in associates and joint ventures	295	276
Other investments	441	362
Deferred tax assets	2,123	2,214
Other non-current assets	721	438
Total non-current assets	14,561	14,021
Current assets		
Inventories	2,437	2,177
Current tax recoverable	186	416
Trade and other receivables	5,317	5,348
Liquid investments	1,035	1,025
Cash and cash equivalents	2,005	4,209
Assets held for sale	12	2
Total current assets	10,992	13,177
TOTAL ASSETS	25,553	27,198
LIABILITIES		
Current liabilities		
Short-term borrowings	(718)	(1,200)
Trade and other payables	(4,871)	(5,147)
Current tax payable	(621)	(2,269)
Short-term provisions	(1,055)	(895)
Total current liabilities	(7,265)	(9,511)
Non-current liabilities		
Long-term borrowings	(4,772)	(5,271)
Deferred tax provision	(595)	(569)
Pensions and other post-employment benefits	(2,339)	(3,069)
Other provisions	(528)	(741)
Other non-current liabilities	(406)	(467)
Total non-current liabilities	(8,640)	(10,117)
TOTAL LIABILITIES	(15,905)	(19,628)
NET ASSETS	9,648	7,570
EQUITY		
Share capital	1,498	1,491
Share premium account	858	549
Other reserves	65	(308)
Retained earnings	6,965	5,579
Shareholders' equity	9,386	7,311
Minority interests	262	259
TOTAL EQUITY	9,648	7,570

RECONCILIATION OF MOVEMENTS IN EQUITY

	2006 £m	2005 £m
Total equity at beginning of year	**7,570**	5,925
Total recognised income and expense for the year	**5,395**	4,576
Dividends to shareholders	**(2,598)**	(2,390)
Shares issued	**316**	252
Shares purchased and held as Treasury shares	**(1,348)**	(1,000)
Consideration received for shares transferred by ESOP Trusts	**151**	68
Share-based incentive plans	**226**	240
Tax on share-based incentive plans	**21**	25
Changes in minority interest shareholdings	**2**	(40)
Distributions to minority shareholders	**(87)**	(86)
Total equity at end of year	**9,648**	7,570

FINANCIAL REVIEW - BALANCE SHEET

Net assets

The book value of net assets increased by £2,078 million from £7,570 million at 31st December 2005 to £9,648 million at 31st December 2006. Net debt increased and the overall tax creditor position decreased following the gross payment of $3.3 billion (£1.8 billion) under the transfer pricing dispute settlement with the US Internal Revenue Service (see 'Taxation' on page 13). The pension and other post-employment liabilities decreased following improvements in asset values, further special contributions to the UK and US pension funds and a strengthening of long-term interest rates, including an increase in the rate used to discount UK pension liabilities from 4.75% to 5.0%.

The carrying value of investments in associates and joint ventures at 31st December 2006 was £295 million, with a market value of £1,020 million.

Equity

At 31st December 2006, total equity had increased from £7,570 million at 31st December 2005 to £9,648 million. The increase arises principally from retained earnings and actuarial gains on defined benefit pension plans in the year partially offset by further purchases of Treasury shares.

At 31st December 2006, the ESOP Trusts held 153.5 million GSK shares against the future exercise of share options and share awards. The carrying value of £1,999 million has been deducted from other reserves. The market value of these shares was £2,062 million. At 31st December 2006, GSK also held 235.5 million shares as Treasury shares, at a cost of £3,147 million, which has been deducted from retained earnings.

CASH FLOW STATEMENT
Year ended 31st December 2006

	2006 £m	2005 £m
Profit after tax	5,498	4,816
Tax on profits	2,301	1,916
Share of after tax profits of associates and joint ventures	(56)	(52)
Finance income/expense	65	194
Depreciation and other non-cash items	1,138	1,103
Increase in working capital	(471)	(323)
(Decrease)/increase in other net liabilities	(272)	11
Cash generated from operations	8,203	7,665
Taxation paid	(3,846)	(1,707)
Net cash inflow from operating activities	4,357	5,958
Cash flow from investing activities		
Purchase of property, plant and equipment	(1,366)	(903)
Proceeds from sale of property, plant and equipment	43	54
Purchase of intangible assets	(224)	(278)
Proceeds from sale of intangible assets	175	221
Purchase of equity investments	(57)	(23)
Proceeds from sale of equity investments	32	35
Share transactions with minority shareholders	(157)	(36)
Purchase of businesses, net of cash acquired	(273)	(1,026)
Disposals of businesses and interests in associates	5	(2)
Investment in associates and joint ventures	(13)	(2)
Interest received	299	290
Dividends from associates and joint ventures	15	10
Net cash outflow from investing activities	(1,521)	(1,660)
Cash flow from financing activities		
(Increase)/decrease in liquid investments	(55)	550
Proceeds from own shares for employee share options	151	68
Issue of share capital	316	252
Purchase of Treasury shares	(1,348)	(999)
Increase in long-term loans	-	982
Repayment of long-term loans	-	(70)
Net repayment of short-term loans	(739)	(857)
Net repayment of obligations under finance leases	(34)	(36)
Interest paid	(414)	(381)
Dividends paid to shareholders	(2,598)	(2,390)
Dividends paid to minority interests	(87)	(86)
Other financing cash flows	16	53
Net cash outflow from financing activities	(4,792)	(2,914)
(Decrease)/increase in cash and bank overdrafts in the year	(1,956)	1,384
Exchange adjustments	(254)	233
Cash and bank overdrafts at beginning of year	3,972	2,355
Cash and bank overdrafts at end of year	1,762	3,972
Cash and bank overdrafts at end of year comprise:		
Cash and cash equivalents	2,005	4,209
Overdrafts	(243)	(237)
	1,762	3,972

CASH FLOW STATEMENT
Three months ended 31st December 2006

	Q4 2006 £m	Q4 2005 £m
Profit after tax	1,205	1,151
Tax on profits	505	455
Share of after tax profits of associates and joint ventures	(13)	(13)
Finance income/expense	3	40
Depreciation and other non-cash items	251	434
Increase in working capital	(11)	(255)
Increase/(decrease) in other net liabilities	6	(92)
Cash generated from operations	1,946	1,720
Taxation paid	(441)	(435)
Net cash inflow from operating activities	1,505	1,285
Cash flow from investing activities		
Purchase of property, plant and equipment	(470)	(348)
Proceeds from sale of property, plant and equipment	11	(9)
Purchase of intangible assets	(69)	(93)
Proceeds from sale of intangible assets	(8)	(3)
Purchase of equity investments	(22)	(5)
Proceeds from sale of equity investments	10	13
Share transactions with minority shareholders	1	(4)
Purchase of businesses, net of cash acquired	(256)	(883)
Disposals of businesses and interests in associates	2	(2)
Investment in associates and joint ventures	(5)	-
Interest received	102	90
Dividends from associates and joint ventures	2	2
Net cash outflow from investing activities	(702)	(1,242)
Cash flow from financing activities		
Increase in liquid investments	(6)	(684)
Proceeds from own shares for employee share options	31	45
Issue of share capital	55	171
Purchase of Treasury shares	(534)	(374)
Net increase in/(repayment of) short-term loans	135	(489)
Net repayment of obligations under finance leases	(7)	(11)
Interest paid	(167)	(60)
Dividends paid to shareholders	(620)	(567)
Dividends paid to minority interests	(6)	(8)
Other financing cash flows	116	21
Net cash outflow from financing activities	(1,003)	(1,956)
Decrease in cash and bank overdrafts in the period	(200)	(1,913)
Exchange adjustments	(46)	20
Cash and bank overdrafts at beginning of period	2,008	5,865
Cash and bank overdrafts at end of period	1,762	3,972
Cash and bank overdrafts at end of period comprise:		
Cash and cash equivalents	2,005	4,209
Overdrafts	(243)	(237)
	1,762	3,972

RECONCILIATION OF CASH FLOW TO MOVEMENTS IN NET DEBT

	2006 £m	2005 £m
Net debt at beginning of the year	**(1,237)**	(1,984)
(Decrease)/increase in cash and bank overdrafts	**(1,956)**	1,384
Cash outflow/(inflow) from liquid investments	**55**	(550)
Net increase in long-term loans	**-**	(912)
Net repayment of short-term loans	**739**	857
Net repayment of obligations under finance leases	**34**	36
Net non-cash funds of businesses acquired	**-**	(68)
Exchange adjustments	**(9)**	39
Other non-cash movements	**(76)**	(39)
(Increase)/decrease in net debt	**(1,213)**	747
Net debt at end of the year	**(2,450)**	(1,237)

FINANCIAL REVIEW - CASH FLOW

Cash generated from operations was £8,203 million in 2006. This represents an increase of £538 million over 2005, principally due to higher operating profits which were partially offset by an increase in working capital and a decrease in other net liabilities. The operating cash flow is in excess of the funds needed for the routine cash flows of tax, capital expenditure on property, plant and equipment and dividend payments, together amounting to £7.8 billion. Taxation paid during the year included the gross payment of $3.3 billion (£1.8 billion) under the transfer pricing dispute settlement with the US Internal Revenue Service (see 'Taxation' on page 13). The purchase of businesses cost £273 million. Receipts of £467 million arose from the exercise of share options: £151 million from shares held by the ESOP Trusts and £316 million from the issue of new shares. In addition, £1,348 million was spent in the year on purchasing the company's shares to be held as Treasury shares.

EXCHANGE RATES

The results and net assets of the Group, as reported in sterling, are affected by movements in exchange rates between sterling and overseas currencies. GSK uses the average of exchange rates prevailing during the period to translate the results and cash flows of overseas Group subsidiary and associated undertakings into sterling and period-end rates to translate the net assets of those undertakings. The currencies which most influence these translations, and the relevant exchange rates, are:

	2006	2005	Q4 2006	Q4 2005
Average rates:				
£/US$	**1.85**	1.82	**1.94**	1.73
£/Euro	**1.47**	1.46	**1.50**	1.46
£/Yen	**215.00**	200.00	**227.00**	203.00
Period-end rates:				
£/US$	**1.96**	1.72	**1.96**	1.72
£/Euro	**1.48**	1.46	**1.48**	1.46
£/Yen	**233.00**	203.00	**233.00**	203.00

During 2006, average sterling exchange rates were stronger against the US dollar, the Euro and the Yen compared with 2005. Comparing 2006 period-end rates with 2005 period-end rates, sterling was stronger against the US dollar, the Euro and the Yen.

LEGAL MATTERS

The Group is involved in various legal and administrative proceedings, principally product liability, intellectual property, tax, anti-trust and governmental investigations and related private litigation concerning sales, marketing and pricing. The Group makes provision for those proceedings on a regular basis and may make additional significant provisions for such legal proceedings, as required in the event of further developments in those matters, consistent with generally accepted accounting principles. Litigation, particularly in the USA, is inherently unpredictable and excessive awards that may not be justified by the evidence can occur. The Group could in the future incur judgments or enter into settlements of claims that could result in payments that exceed its current provisions by an amount that would have a material adverse effect on the Group's financial condition, results of operations and cash flows.

Intellectual property claims include challenges to the validity of the patents on various of the Group's products or processes and assertions of non-infringement of those patents. A loss in any of these cases could result in loss of patent protection for the product at issue. The consequence of any such loss could be a significant decrease in sales of that product and could materially affect future results of operations for the Group.

At 31st December 2006, the Group's aggregate provision for legal and other disputes (not including tax matters described under 'Taxation' on page 13) was over £1.1 billion. The ultimate liability for legal claims may vary from the amounts provided and is dependent upon the outcome of litigation proceedings, investigations and possible settlement negotiations.

Developments since the date of the Annual Report as previously updated by the Legal matters sections of the Results Announcements for the first, second and third quarters of 2006 include:

Intellectual property

With respect to the Group's application to the US Patent and Trademark Office (USPTO) for re-issue of its combination patent for *Advair*, in January 2007 the Group received a Notice of Allowance finding the pharmaceutical composition claims patentable. The re-issue patent will have the same September 2010 expiration date as the original combination patent. In addition, the Group holds other US patents relating to *Advair*, including various patents relating to the *Diskus* device which expire over a period from 2011 to 2016, and various patents relating to the HFA formulation and MDI device which expire over a period from 2014 to 2017.

With respect to the Group's patent infringement action against Cobalt Pharmaceuticals in respect of *Imitrex*, the Group reached a settlement with Cobalt in November 2006 which provides that Cobalt may distribute a generic version of sumatriptan tablets in the USA with an expected launch date early in the first quarter of 2009.

With respect to the Group's patent infringement action against Spectrum Pharmaceuticals in respect of *Imitrex*, the Group reached a settlement with Spectrum in December 2006 which provides that Spectrum may exclusively distribute authorised generic versions of certain sumatriptan injection products in the USA with an expected launch during GSK's sumatriptan paediatric exclusivity period which begins in August 2008, with such launch occurring not later than early November 2008.

With respect to the trial of the Group's patent infringement action in respect of *Requip* against Teva Pharmaceuticals in the US District Court for the District of Delaware, in December 2006 the judge ruled at the conclusion of the trial that the Group's patent on the use of ropinirole (the active ingredient in *Requip*) to treat Parkinson's disease is novel and non-obvious rejecting Teva's claims on those grounds. Teva's further claim that the patent is unenforceable for inequitable conduct remains before the judge as the evidence was not reviewed at the trial. This issue is to be decided on the basis of deposition testimony and documents and consideration of further potential filings by the parties. Teva's original challenge to the Group's basic compound patent was withdrawn before the trial, and Teva has accepted that the FDA will not approve its product prior to expiration of that patent.

With respect to the Group's patent infringement action against Ranbaxy Laboratories in respect of *Valtrex*, on 1st February 2007, Ranbaxy received FDA approval for its generic valacyclovir product, and notified the Group that it sought to market the product in the USA. The Group will apply to the court for a preliminary injunction prohibiting launch of this product pending completion of the lawsuit. Under the terms of an agreement between the companies, previously approved by the court, if the Group applies for such an injunction within 45 days, Ranbaxy will not launch its product until the court either rules on the preliminary injunction or decides the pending court case. No trial date has yet been set for the pending court case.

With respect to *Wellbutrin XL*, the US Food and Drug Administration (FDA) has approved Abbreviated New Drug Applications for Anchen Pharmaceuticals for a generic form of *Wellbutrin XL* (150mg and 300mg tablets) and Impax Laboratories for a generic form of 300mg tablets. Marketing of a 300mg tablet generic version of *Wellbutrin XL* began in December 2006.

With respect to the Group's patent infringement action against Teva Pharmaceuticals in the US District Court for the District of New Jersey in respect of the basic compound patent (expiring in 2012) and the maleate salt patent (expiring in 2015) for *Avandia*, a trial date has been set for 6th August 2007. Dr Reddy's Laboratories' challenge of the maleate salt patent in the same court has been combined with the Teva action for trial. Neither Dr Reddy's nor the other manufacturers that have filed ANDAs for generic forms of *Avandia* have challenged the validity of the basic compound patent.

Anti-trust

With respect to anti-trust actions initiated against the Group on the basis of the Group's actions in 2003 to reduce illegal importation of prescription drugs from Canada, in November 2006 the US Court of Appeals for the Eighth Circuit affirmed the decision of the US District Court for the District of Minnesota which had granted the Group's motion to dismiss the purported class actions that had been consolidated for trial before that court. In December 2006, the trial judge, for the California state court anti-trust action filed on behalf of a number of retail pharmacies, granted the Group's motion for summary judgment. The remaining state anti-trust case filed by the Minnesota state attorney general is still in the discovery phase.

Commercial and other litigation

In December 2006, two purported class actions were filed in the US District Courts for the Central and Southern Districts of California against the Group on behalf of all the Group's US pharmaceutical sales representatives alleging that those representatives are entitled to overtime pay. Similar actions have been filed against other pharmaceutical companies. The cases are in their early stages.

Developments with respect to tax matters are described in 'Taxation' on page 13.

ACCOUNTING PRESENTATION AND POLICIES

This unaudited Results Announcement containing condensed financial information for the twelve and three months ended 31st December 2006 is prepared in accordance with the Listing Rules of the London Stock Exchange, IAS 34 'Interim Financial Reporting' and the accounting policies set out in the Annual Report 2005, except that IFRIC Interpretation 4 'Determining whether an arrangement contains a lease' and an amendment to IAS 39 'Financial guarantee contracts' have been implemented in 2006. Neither change has had a material effect on the current or prior periods. This Results Announcement does not constitute statutory accounts of the Group within the meaning of section 240 of the Companies Act 2005.

The income statement, statement of recognised income and expense and cash flow statement for the year ended, and the balance sheet at, 31st December 2005 have been derived from the full Group accounts published in the Annual Report 2005, which have been delivered to the Registrar of Companies and on which the report of the independent auditors was unqualified and did not contain a statement under either section 237(2) or section 237(3) of the Companies Act 1985.

Data for market share and market growth rates are GSK estimates based on the most recent data from independent external sources and, where appropriate, are valued in sterling at relevant exchange rates. Figures quoted for product market share reflect sales by GSK and licensees.

In order to illustrate underlying performance, it is the Group's practice to discuss its results in terms of constant exchange rate (CER) growth. This represents growth calculated as if the exchange rates used to determine the results of overseas companies in sterling had remained unchanged from those used in the previous year. All commentaries are presented in terms of CER unless otherwise stated.

INVESTOR INFORMATION

Preliminary Announcement of Annual Results for 2006
This Announcement was approved by the Board of Directors on Thursday 8th February 2007.

The income statement, statement of recognised income and expense, and cash flow statement for the year ended 31st December 2006 and the balance sheet at that date, are subject to completion of the audit and may also change should a significant adjusting event occur before the approval of the Annual Report 2006 on 28th February 2007.

Financial calendar
The company will announce first quarter 2007 results on 25th April 2007. The first interim dividend for 2007 will have an ex-dividend date of 2nd May 2007 and a record date of 4th May 2007. It will be paid on 12th July 2007.

Internet
This Announcement and other information about GSK are available on the company's website at: http://www.gsk.com.

EXHIBIT 26

FDA News

FOR IMMEDIATE RELEASE
P07-88
May 21, 2007

Media Inquiries:
Susan Cruzan, 301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA Issues Safety Alert on Avandia

The U.S. Food and Drug Administration (FDA) is aware of a potential safety issue related to Avandia (rosiglitazone), a drug approved to treat type 2 diabetes. Safety data from controlled clinical trials have shown that there is a potentially significant increase in the risk of heart attack and heart-related deaths in patients taking Avandia. However, other published and unpublished data from long-term clinical trials of Avandia, including an interim analysis of data from the RECORD trial (a large, ongoing, randomized open label trial) and unpublished reanalyses of data from DREAM (a previously conducted placebo-controlled, randomized trial) provide contradictory evidence about the risks in patients treated with Avandia.

Patients who are taking Avandia, especially those who are known to have underlying heart disease or who are at high risk of heart attack should talk to their doctor about this new information as they evaluate the available treatment options for their type 2 diabetes.

FDA's analyses of all available data are ongoing. FDA has not confirmed the clinical significance of the reported increased risk in the context of other studies. Pending questions include whether the other approved treatment from the same class of drugs, pioglitazone, has less, the same or greater risks. Furthermore, there is inherent risk associated with switching patients with diabetes from one treatment to another even in the absence of specific risks associated with particular treatments. For these reasons, FDA is not asking GlaxoSmithKline, the drug's sponsor, to take any specific action at this time. FDA is providing this emerging information to prescribers so that they, and their patients, can make individualized treatment decisions.

"FDA remains committed to assuring that doctors and patients have the latest information available to make treatment and medication use decisions. In this case, FDA is carefully weighing several complex sources of data, some of which show conflicting results, related to the risk of heart attack and heart-related deaths in patients treated with Avandia," said Steven Galson, M.D., M.P.H., director of FDA's Center for Drug Evaluation and Research. "We will complete our analyses and make the results available as soon as possible. FDA will take the issue of cardiovascular risk associated with Avandia and other drugs in this class to an Advisory Committee as soon as one can be convened."

Avandia was approved in 1999 for treatment of type 2 diabetes, a serious and life threatening disease that affects about 18 to 20 million Americans. Diabetes is a leading cause of coronary heart disease, blindness, kidney failure and limb amputation. Since the drug was approved, FDA has been monitoring several heart-related adverse events (e.g., fluid retention, edema and congestive heart failure) based on signals seen in previous controlled clinical trials of Avandia alone and in combination with other drugs, and from postmarketing reports. FDA has updated the product's labeling on several occasions to reflect these new data, most recently in 2006. The most recent labeling change for Avandia also included a new warning about a potential increase in heart attacks and heart-related chest pain in some individuals using Avandia. This new warning was based on the result of a controlled clinical trial in patients with existing congestive heart failure.

Recently, the manufacturer of Avandia provided FDA with a pooled analysis (meta analysis) of 42 randomized, controlled clinical trials in which Avandia was compared to either placebo or other anti-diabetic therapies in patients with type 2 diabetes. The pooled analysis suggested that patients receiving short-term (most studies were 6-months duration) treatment with Avandia may have a 30-40 percent greater risk of heart attack and other heart-related adverse events than patients treated with placebo or other anti-diabetic therapy. These data, if confirmed, would be of significant concern since patients with diabetes are already at an increased risk of heart disease.

Avandia is manufactured by GlaxoSmithKline, which is based in Research Triangle Park, N.C.

Additional Information

RSS Feed for FDA News Releases [what's this?]

Get free weekly updates about FDA press releases, recalls, speeches, testimony and more.

EXHIBIT 27

European Medicines Agency
Press office

London, 23 May 2007
Doc. Ref. EMEA/230057/2007

PRESS RELEASE

EMEA statement on recent publication on cardiac safety of rosiglitazone (Avandia, Avandamet, Avaglim)

An article published in the New England Journal of Medicine (NEJM) has raised concern about a small increased risk of myocardial infarction and cardiovascular death in patients with type 2 diabetes treated with rosiglitazone. The article, based on an analysis of data retrieved from 42 clinical studies, showed a small increased risk for myocardial infarction and cardiovascular death among approximately 15,500 patients treated with rosiglitazone. However, death from all causes was not significantly increased.

When rosiglitazone was first authorised in the EU in 2000, it was contraindicated in patients with a history of cardiac failure. Since then, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has kept rosiglitazone under close surveillance for cardiovascular effects (cardiac failure and other cardiac disorders including myocardial infarction). The majority of the studies included in the NEJM paper have already been assessed by the CHMP. The EU product information was updated in September 2006 with information about the risk of cardiac ischaemic events.

Some of the studies in the NEJM paper included patients who were not treated in line with the indication approved in the EU. Prescribers are reminded to adhere to the restrictions for use in patients with cardiac disease as set out in the product information.

Patients are advised not to stop treatment with rosiglitazone and to discuss the medication with their doctor at their next regular visit.

--ENDS--

NOTES

1. The article 'Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes' (10.1056/NEJMoa072761) was published on the NEJM website (www.nejm.org) on 21 May 2007.
2. The rosiglitazone-containing products Avandia (rosiglitazone maleate) Tablets, Avandamet (rosiglitazone maleate and metformin hydrochloride) Tablets, and Avaglim (rosiglitazone maleate and glimepiride) Tablets are centrally authorised products and indicated for treatment of type 2 diabetes mellitus as monotherapy or in combination with other oral antidiabetic drugs. Avandia was first authorised in the EU in July 2000; Avandamet in October 2003; Avaglim in June 2006.
3. The European Public Assessment Reports including the up-to-date product information are available on the EMEA website as follows:
   Avandia: http://www.emea.europa.eu/humandocs/Humans/EPAR/avandia/avandia.htm
   Avandamet: http://www.emea.europa.eu/humandocs/Humans/EPAR/avandamet/avandamet.htm
   Avaglim: http://www.emea.europa.eu/humandocs/Humans/EPAR/avaglim/avaglim.htm
4. This press release, together with other information about the work of the EMEA, may be found on the EMEA website: http://www.emea.europa.eu

Media enquiries only please contact:
Martin Harvey Allchurch or Monika Benstetter
Tel. (44-20) 74 18 84 27, E-mail: press@emea.europa.eu

EXHIBIT 28

This is a revised version of a FDA Press Release, originally issued November 14, 2007. Revisions have been made to correct the title from "Heart Attacks to Heart-related Risk.

FDA News

FOR IMMEDIATE RELEASE

November 14, 2007

Media Inquiries:
Susan Cruzan, 301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA Adds Boxed Warning for Heart-related Risks to Anti-Diabetes Drug Avandia

Agency says drug to remain on market, while safety assessment continues

The U.S. Food and Drug Administration announced today that the manufacturer of Avandia (rosiglitazone), a drug used to treat type 2 diabetes, has agreed to add new information to the existing boxed warning in the drug's labeling about potential increased risk for heart attacks.

People with type 2 diabetes who have underlying heart disease or who are at high risk of heart attack should talk with their health care provider about the revised warning as they evaluate treatment options. FDA advises health care providers to closely monitor patients who take Avandia for cardiovascular risks.

"FDA has moved expeditiously to review the cardiovascular risks of this drug so that we could inform patients and doctors at the earliest possible time of our findings," said Janet Woodcock, M.D., FDA's deputy commissioner for scientific and medical programs, chief medical officer, and acting director of the Center for Drug Evaluation and Research. "FDA remains committed to making sure that doctors and patients have the latest information about the risks and benefits of medicines."

Avandia, manufactured by GlaxoSmithKline (GSK), Philadelphia, Pa., was approved in 1999 as an adjunct to diet and exercise to improve control of blood sugar levels. Avandia is approved to be used as a single therapy or used in combination with metformin and sulfonylureas, other oral anti-diabetes treatments.

During the past year, FDA has carefully weighed several complex sources of data, some which show conflicting results, related to the risk of chest pain, heart attacks and heart-related deaths, and deaths from any cause in patients treated with Avandia.

At this time, FDA has concluded that there isn't enough evidence to indicate that the risks of heart attacks or death are different between Avandia and some other oral type 2 diabetes treatments. Therefore, FDA has requested that GSK conduct a new long-term study to evaluate the potential cardiovascular risk of Avandia, compared to an active control agent. GSK has agreed to conduct the study and FDA will ensure it is initiated promptly.

The revision of Avandia's existing boxed warning – FDA's strongest form of warning – includes the following statement:

A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared Avandia to placebo, showed Avandia to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 patients), comparing Avandia to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.

The previous upgraded warning, added to certain diabetes drugs (in class of drugs related to Avandia) on Aug. 14, 2007, emphasized that these types of drugs may worsen heart failure, a condition in which the heart does not adequately pump blood, in some patients.
GSK is also developing a Medication Guide for patients to provide additional information about the benefits and risks and safe use of Avandia.

To date, no oral anti-diabetes drug has been conclusively shown to reduce cardiovascular risk. Consequently, the agency also will be requesting that labeling of all approved oral anti-diabetes drugs contain language describing the lack of data showing this benefit.

Today's action follows recommendations made at the July 2007 joint meeting of FDA's Endocrine and

Metabolic Drugs and Drug Safety and Risk Management Advisory Committees. At the meeting, members voted 22-1 to recommend that Avandia stay on the market, pending a review of additional data. The committee also advised that information warning of the potential for increased risk of heart attacks should be added to the drug labeling.

For more information:
Rosiglitazone maleate (marketed as Avandia, Avandamet, and Avandaryl) Information
www.fda.gov/cder/drug/infopage/rosiglitazone/default.htm

FDA Issues Safety Alert on Avandia
www.fda.gov/bbs/topics/NEWS/2007/NEW01636.html

#

EXHIBIT 29

GlaxoSmithKline revises US labeling for Avandia

Print
Close

Issued – Wednesday 14 November 2007, London, UK & Philadelphia, US

GlaxoSmithKline revises US labeling for Avandia®

GlaxoSmithKline announced today that it is implementing changes to the US product label for *Avandia*® (rosiglitazone maleate), based on an extensive and thorough review by the FDA of myocardial ischemia data on *Avandia*, the most widely studied oral anti-diabetic medicine available.

The existing boxed warning has been revised to add the FDA's conclusion that, while an FDA meta-analysis of short-term studies – mostly against placebo - showed an association between *Avandia* and an increase in myocardial ischemic events, that risk was not confirmed or excluded in three long-term clinical trials comparing *Avandia* against both placebo and other oral anti-diabetes medicines. The box will state that the available data on the risk of myocardial ischemia are inconclusive.

The FDA has also concluded there is insufficient information available to determine whether any oral anti-diabetic medicine reduces cardiovascular risk. The FDA has directed that the sentence - "There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with *Avandia* or any other oral antidiabetic drugs" - will be added as a warning on the labels of all oral anti-diabetic medicines.

The *Avandia* label also has been updated to add that *Avandia* is not recommended - though not contraindicated - for use with patients who are taking insulin or nitrates. The label summarizes the data on myocardial ischemia to help doctors continue to evaluate which patients could benefit from taking *Avandia*, and those for whom alternative treatment should be considered.

The changes are now included in labeling for *Avandia*, and will be incorporated into future revised labeling for all approved rosiglitazone-containing products, including *Avandamet* (rosiglitazone maleate and metformin hydrochloride), and *Avandaryl* (rosiglitazone maleate and glimepiride). GSK is also preparing a Medication Guide to help educate patients about potential benefits and risks and to provide other information on *Avandia*.

"*Avandia* remains a valuable medicine for most patients with type 2 diabetes, and when used according to the labeling, has a well described and appropriate safety and effectiveness profile," said Dr. Ronald Krall, GSK Chief Medical Officer. "Given the severity of this disease and the importance of *Avandia* in helping patients manage their diabetes, we will continue to work with the FDA to conduct more studies about the safety and benefits of our medicine."

As previously stated by GSK, two long-term trials in diabetic patients comparing *Avandia* to other oral anti-diabetic medicines show no increased risk for cardiovascular events compared to other commonly used medications, other than the well-known risk of congestive heart failure with TZDs. One trial – ADOPT - shows no increased myocardial ischemic risk compared to metformin or sulfonylurea. The interim results of a second long-term trial – RECORD - also show no increased risk of major cardiovascular events (death, heart attack and stroke) between *Avandia* and other medications; however, firm conclusions cannot be drawn because the trial has not yet been completed. The updated label includes data from ADOPT and RECORD plus a third long-term trial in pre-diabetic patients (DREAM). The combined analysis of these three studies show there was no increased risk of *Avandia* over

comparatorswith regard to myocardial infarction, mortality, or other non-heart failure cardiovascular events.

GSK believes data from ongoing and future clinical trials will provide additional scientific support for both the benefit and safety of *Avandia*. GSK has agreed to work with the FDA to plan and carry out a clinical trial to further investigate the cardiovascular effects of *Avandia*.

*Avandia*has been prescribed to more than seven million people over the last seven years to help them control their blood sugar levels. Importantly, *Avandia* has been shown to control blood sugar for longer than the most commonly used oral enti-diabetic medicines – up to five years. Long-term glycemic control is important to help prevent the serious complications of diabetes, especielly microvascular complications leading to blindness, amputation and kidney failure. *Avandia* is an important treatment option for physicians, since two-thirds of diabetic patients suffer with uncontrolled disease end many require two or three medicines to maintain their blood sugar.

GlaxoSmithKline — one of the world's leading research-based pharmaceutical and healthcare companies — is committed to improving the quality of human life by enabling people to do more, feel better and live longer. For company information, visit GlaxoSmithKline on the World Wide Web at www.gsk.com.

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Important Safety Information for *Avandia*® (rosiglitazone maleate)

Avandia, along with diet and exercise, helps improve blood sugar control in patients with type 2 diabetes.

*Avandia*can cause or worsen heart failure. If you have severe heart failure (very poor pumping ability of the heart), you cannot be started on *Avandia*. *Avandia* is also not recommended if you have heart failure with symptoms (such as shortness of breath or swelling) even if these symptoms are not severe.

*Avandia*may increase your risk of other heart problems that occur when there is reduced blood flow to the heart, such as chest pain (angina) or heart attack (myocardial infarction). This risk appeared

higher in patients taking medicines called nitrates or insulin. Taking *Avandia* with insulin or with nitrates is not recommended.

If you have chest pain or a feeling of chest pressure, you should seek immediate medical attention, regardless of what diabetes medicines you are taking.

If you take *Avandia*, tell your doctor right away if you:

· Have swollen legs or enkles, a rapid increase in weight or difficulty breathing, or unusual tiredness

· Experience changes in vision

· Become pregnant

Review your medical history and tell your doctor if you:

· Have heart failure or other heart problems

· Have liver problems or liver disease

· Are pregnant or are nursing

Women taking *Avandia* should know that *Avandia* may increase the risk of pregnancy.

More fractures have been observed in women taking *Avandia*.

For more information about *Avandia*, please see Patient Information. For further information on *Avandia*, please see full Prescribing Information.

Cautionary statement regarding forward-looking statements

Under the safe harbor provisions of the US Private Securities Litigation Reform Act of 1995, the company cautions investors that any forward-looking statements or projections made by the company, including those made in this Announcement, are subject to risks and uncertainties that may cause actual results to differ materially from those projected. Factors that may affect the company's operations are described under 'Risk Factors' in the 'Business Review' in the company's Annual Report 2006.

EXHIBIT 30

Procedural steps taken and scientific information after the authorisation
Changes made after 01/09/2003

Avandia

For procedures finalised before 01/09/2003, please refer to module 8A

MAJOR CHANGES[1]

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
II/0052	Update of section 4.3 of the Summary of Products Characteristics (SPC) in order to remove the contra-indication for the use of Avandia in combination with insulin. Consequently a contra-indication with diabetic ketoacidosis or diabetic pre-coma was added to the same section. Additionally, section 4.4 of the SPC has been updated with warnings regarding the risks of the use of rosiglitazone in combination with insulin. The Package Leaflet has been amended accordingly.	18/10/2007	21/11/2007	SPC, PL	Please refer to the scientific discussion Avandia-H-C-268-II-52 scientific discussion
II/0053	Update of Section 4.4 and Section 4.8 of the SPC to inform prescribers about new safety information concerning bone fractures following analysis of a long term efficacy and safety study (Study ADOPT). The corresponding sections of the Patient Leaflet have been appropriately revised.	26/04/2007	30/05/2007	SPC, PL	The results of a randomised, double-blind, parallel group study (ADOPT) of 4,360 patients with recently diagnosed type 2 diabetes mellitus whose progression of diabetes was followed for 4-6 years were recently published (Kahn et al., 2006). Data showed that more female patients who received rosiglitazone experienced fractures (mainly of the upper arm, hand and foot) than did female patients who received either metformin or glibenclamide. The observed incidence of fractures for male patients in ADOPT was similar among the treatment groups. Wording has been included in sections 4.4 and 4.8 of the SPC for rosiglitazone-containing products to reflect this new information, with update to the relevant sections of the Package Leaflet.

[1] Major changes e.g. Type II variations, Annex II applications, Renewals and Annual Reassessments
[2] SPC (Summary of Product Characteristics), Labelling, PL (Package Leaflet)

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
II/0048	The Marketing Authorisation Holder applied for an update of section 4.8 of the Summary of Product Characteristics to add the skin reactions 'pruritis' and 'rash' and the event 'anaphylactic reaction'. The Package Leaflet has been updated accordingly.	18/10/2006	22/11/2006	SPC, PL	The MAH applied for this variation to include information regarding skin reactions (pruritis and rash) and anaphylactic reaction in section 4.8 of the SPC, and related changes in the Package Leaflet. In the post-marketing data review, 25 pivotal reports were identified of which, 12 reported pruritis, 16 reported rash/drug eruption, 4 described urticaria, and 3 described anaphylactic reaction/Type III immune complex reaction. These 25 pivotal reports were evaluated based on the criteria for diagnosis of a drug reaction. Nine of the 25 reports described the time to onset to be 3 days or less. Three additional reports described the time to onset to be 9 to 21 days. All 25 of these pivotal reports described a positive rechallenge. After review of the post-marketing data, seven reports of anaphylactic reaction were identified. All of these seven reports were from spontaneous sources, one of which was a consumer report. Four of these seven reports described the onset of the anaphylactic reaction to be within two days following the start of therapy. The remaining three reports described the onset as 21 days, 19 months and "several weeks". Six of the seven reports were serious and one was considered non-serious. None of these seven reports described a fatal outcome. Two of the seven anaphylactic events described a positive rechallenge during RSG use. Although Rosiglitazone causes skin and anaphylactic reactions, the majority of the skin reactions were non-serious, in contrast to the anaphylactic reactions. Therefore, the presented data do not change the overall risk/benefit assessment. The CHMP concluded that the SPC and PL should be updated to reflect the mentioned data.
II/0047	Update of Summary of Product Characteristics and Package Leaflet Update of sections 4.2, 4.4 and 4.8 of the	21/09/2006	24/10/2006	SPC, PL	The Marketing Authorisation Holder (MAH) applied in this type II variation for the update of the sections 4.2, 4.4, 4.8 of the SPC, and related sections of the PL, following analysis of cardiovascular events using

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
	Summary of Product Characteristics (SPC) to include information on cardiovascular events following a comprehensive review of data from clinical trials and an epidemiological study. The relevant sections 2 and 4 of the Package Leaflet (PL) have been updated accordingly.				an integrated dataset of 42 rosiglitazone clinical trials, and data from an epidemiological study that evaluated the relative risk of myocardial infarction and coronary revascularization in adults with type 2 diabetes initiating rosiglitazone in clinical practice. The MAH has provided new data concerning the risk for congestive heart failure in patients treated with rosiglitazone, especially in combination with a sulphonylurea or insulin. The results also indicate that there could be a risk for ischaemic cardiac events. Even if epidemiological data do not support this, the CHMP concluded that this particular risk can not be ruled out. As a consequence the MAH wished to update the SPC with information regarding these risks. Sections 4.2, 4.4, 4.8 of the SPC and 2, 4 of the PL have been updated.
II/0046	Update of Summary of Product Characteristics Update of the section 4.6 of the Summary of Product Characteristics, following the publication of literature which concluded that rosiglitazone crosses the placenta in the first trimester of human pregnancy.	21/09/2006	24/10/2006	SPC	The Marketing Authorisation Holder (MAH) applied in this type II variation for the update of section 4.6 of the SPC in line with published literature that concluded that rosiglitazone crosses the placenta in the first trimester of human pregnancy. In that respect the following statement was added in the section 4.6 of the SPC (Rosiglitazone has been reported to cross the human placenta and to be detectable in foetal tissues).
II/0044	Update of Summary of Product Characteristics and Package Leaflet This variation refers to an update of Sections 4.4 (Special warnings and special precautions for use) and 4.8 (Undesirable Effects) of the Summary of Product Characteristics (SPC) in relation to cases of macular oedema reported in patients treated with thiazolidinediones including rosiglitazone. The package leaflet (PL) has been updated accordingly.	01/06/2006	12/07/2006	SPC, PL	The MAH received 29 reports of new onset and worsening macular oedema in patients treated with rosiglitazone. 22 reports were identified as key reports. 20 of which were received from the United States. Of these 22 key cases, the majority reported concurrent peripheral oedema. In about half of the cases, macular oedema developed within 3 months of initiation or uptitration of rosiglitazone treatment. In ten cases, rosiglitazone was used concurrently with insulin, which is a contraindicated combination in the EU. The majority of cases had a history of risk factors of macular oedema. In some cases, the macular oedema resolved or improved following discontinuation of therapy and in one case macular

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
					oedema resolved after dose reduction. It is unclear whether or not there is a direct association between rosiglitazone and macular oedema but prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity and appropriate ophthalmologic referral should be considered. The SPC (sections 4.4 and 4.8) and the Package Leaflet (sections 2 and 4) has been updated to reflect this information.
II/0043	Update of section 4.8 (Undesirable Effects) of the Summary of Product Characteristics (SPC) and relevant sections of the Package Leaflet (PL).	27/04/2006	31/05/2006	SPC, Labelling, PL	Following a review of the rosiglitazone safety information reported in 22 clinical studies and from post-marketing data, the MAH applied to revise section 4.8 (Undesirable Effects) of the SPC and relevant sections of the PL.
R/0033	Renewal of the marketing authorisation	21/04/2005	08/07/2005	SPC, Labelling, PL	
II/0032	Update of Summary of Product Characteristics Update of sections 4.2, 5.1 and 5.2 of the Summary of Product Characteristics to reflect the paediatric experience with rosiglitazone derived from an active controlled clinical trial (rosiglitazone up to 8 mg daily or metformin up to 2,000 mg daily) of 24 weeks duration performed in 197 children (10-17 years of age) with type 2 diabetes.	23/06/2005	27/07/2005	SPC	The results of the peadiatric study showed that improvement in HbA1c from baseline achieved statistical significance only in the metformin group. Rosiglitazone failed to demonstrate non-inferiority to metformin. Following rosiglitazone treatment, there were no new safety concerns noted in children compared to adult patients with type 2 diabetes mellitus. A population pharmacokinetic analysis including 96 paediatric patients aged 10 to 18 years and weighing 35 to 178 kg suggested similar mean CL/F in children and adults. Individual CL/F in the paediatric population was in the same range as individual adult data. CL/F seemed to be independent of age, but increased with weight in the paediatric population. The available data do not support efficacy in the paediatric population and therefore such use is not recommended. Sections 4.2, 5.1 and 5.2 of the SPC have been updated to reflect this information.

II/0031	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.8 of the Summary of Product Characteristics (SPC) to include information on the incidence of worsening or possible worsening of heart failure in a placebo-controlled one-year trial in patients with congestive heart failure NYHA class I-II. Additionally, the Marketing Authorisation Holder (MAH) took the opportunity to include a statement that not all pack sizes may be marketed in section 6.5 of the SPC and section 1 of the Package Leaflet (PL) in accordance with the current QRD templates. Also a combined labelling text, combining the different pack-sizes of the same strength, was introduced.	21/04/2005	10/06/2005	SPC, PL	As a commitment to CHMP at the time of the initial marketing authorisation, the MAH undertook to perform a placebo-controlled clinical trial in patients with congestive heart failure NYHA I-II (trial 211). In the one-year trial (trial 211), worsening or possible worsening of heart failure occurred in 6.4% of patients treated with rosiglitazone, compared with 3.5% on placebo. In view of these findings, the currently approved contraindications and warnings and precautions remained unchanged, and section 4.8 of the SPC has been updated to reflect the results from trial 211.
II/0027	Quality changes The Marketing Authorisation Holder applied to revise the specifications for the film coating of Avandia film coated tablets.	21/10/2004	22/10/2004		
II/0026	Update of Summary of Product Characteristics and Package Leaflet The Marketing Authorisation Holder applied to remove the requirement for routine liver enzyme monitoring every two months during the first year of rosiglitazone therapy in section 4.4 of the Summary of Product Characteristics based on clinical trial and post-marketing data. The Package Leaflet has been updated accordingly.	18/11/2004	10/01/2005	SPC, PL	The MAH applied to remove the requirement for routine liver enzyme monitoring every two months during the first year of rosiglitazone therapy in section 4.4 of the SPC based on clinical trial and post-marketing data. The CHMP agreed that there is an acceptable benefit/risk for lifting the requirement for periodic on-therapy liver function test monitoring with rosiglitazone. In order to better follow the effects in the market situation of this amendment the MAH was requested to provide yearly reports on hepato-biliary adverse reactions, especially hepatitis and acute liver failure, and including the adjudication on events of liver failure. The Package Leaflet has been updated accordingly.

II/0025	Update of Summary of Product Characteristics and Package Leaflet Update of sections 4.4 and 4.5 of the Summary of Product Characteristics (SPC) to include data relating to interactions between rosiglitazone and gemfibrozil and to reflect the reported drug interaction between rosiglitazone and rifampicin. The Package Leaflet has been updated accordingly. In addition the Marketing Authorisation Holder applied to update the contact details of the Estonian local representative in the Package Leaflet.	18/11/2004	10/01/2005	SPC, PL	The lipid lowering agent gemfibrozil has previously been shown to reduce the clearance of substrates metabolised by CYP2C9, 2C19, 1A2, 2C8, and UGT 1A1 and/or 1A3 (Preuksaritanont, 2002). In August 2003, the literature featured a single-dose rosiglitazone and a repeat-dose gemfibrozil pharmacokinetic (PK) study (Niemi, 2003), which was conducted in 10 healthy volunteers. Gemfibrozil increased the mean area under the plasma rosiglitazone concentration-time curve (AUC) 2.3-fold (range 1.5- to 2.8-fold); and prolonged the elimination half-life (t½) of rosiglitazone from 3.6 to 7.6 hours. The peak plasma rosiglitazone concentration (Cmax) was increased only 1.2-fold (range 0.9- to 1.6-fold). Following this publication, the MAH also performed a study to investigate the interaction between gemfibrozil and rosiglitazone (BRL-049653/902). On request from the CHMP the MAH applied for this type II variation to update sections 4.4 and 4.5 of the SPC to reflect the interaction data of the publication and the MAH's interaction study. A publication (Park, 2004) reported a 65% decrease in the AUC for rosiglitazone when co-administered with rifampicin, an inducer of CYP2C8 and the intestinal and hepatic CYP enzyme system (Finch 2002). The MAH was requested to incorporate the findings of this study in the SPC (sections 4.4 and 4.5) to provide recommendations on concomitant use of rosiglitazone with CYP inducers. The Package Leaflet has been updated accordingly to reflect this information.

II/0023	Extension of Indication Extension of indication and posology change: To increase the maximum approved rosiglitazone (RSG) dose to 8mg/day in combination with sulphonylurea (SU), and to add a triple oral combination indication for rosiglitazone with metformin (MET) and sulphonylurea, based on new clinical data.	18/11/2004	10/01/2005	SPC, PL	The change to increase the maximum approved RSG dose to 8 mg/day in combination with SU was supported by efficacy and safety data from 12 clinical studies. An incremental benefit in glycaemic control was seen in a meta-analysis comparing 4mg RSG and 8mg RSG in combination with an SU. This is in line with the dose-ordered effect of RSG, which has been described in monotherapy and in add-on therapy to MET. It was also noted that the potential for hypoglycaemia in combination with SU, either dual or triple therapy, warranted mention in section 4.4. In addition section 5.1 of the SPC has been updated to reflect 18-month interim data from an ongoing CHMP commitment study to assess the long-term effects of RSG on cardiovascular outcomes (RECORD). For detailed discussion of the additional indication, triple oral therapy, please refer to the scientific discussion: Avandia-H-268-II-23
II/0021	Update of Summary of Product Characteristics and Package Leaflet	03/06/2004	19/07/2004	SPC, Labelling, PL	Update to bring Product Information in accordance with the QRD templates, CHMP Note for Guidance on Declaration of Storage Conditions, Guideline on the Excipients in the Label and Package Leaflet of Medicinal products for Human Use.

MINOR CHANGES[3]

No	Scope	Product Information affected[2]	Date[4]
IA/0056	11_a_Change in batch size of active substance or intermediate - up to 10-fold		14/11/2007
IA/0055	05_Change in the name and/or address of a manufacturer of the finished product		05/10/2007
IA/0054	09_Deletion of manufacturing site		05/10/2007
IB/0051	07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release		22/11/2006
IB/0050	33_Minor change in the manufacture of the finished product 31_b_Change to in-process tests/limits during manufacture - addition of new tests/limits		07/09/2006
IB/0049	07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release		07/09/2006
IA/0045	07_a_Replacement/add. of manufacturing site: Secondary packaging site		18/04/2006
IB/0042	41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	SPC, Labelling, PL	18/11/2005
IB/0041	41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	SPC, Labelling, PL	18/11/2005
N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	PL	25/10/2005
IA/0039	47_b_Deletion of a strength	SPC, Labelling, PL	11/10/2005
IB/0038	33_Minor change in the manufacture of the finished product		27/04/2005
IA/0037	32_b_Change in batch size of the finished product - downscaling down to 10-fold		13/04/2005
IA/0036	08_a_Change in BR/QC testing - repl./add. of batch control/testing site		13/04/2005
IB/0035	07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release		13/05/2005
IA/0034	39_Change/addition of imprints, bossing or other markings	SPC, PL	13/04/2005
IA/0030	36_b_Change in shape or dimensions of the container/closure - other pharm. forms		07/12/2004
IA/0029	07_a_Replacement/add. of manufacturing site: Secondary packaging site		27/11/2004
IA/0028	07_a_Replacement/add. of manufacturing site: Secondary packaging site		22/11/2004
IB/0024	30_b_Change in supplier of packaging components - replacement/addition		13/07/2004
N/0022	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	PL	28/05/2004
IB/0020	10_Minor change in the manufacturing process of the active substance		30/03/2004

[3] Minor changes e.g. Type I variations and Notifications
[4] Date of entry into force of the change

EXHIBIT 31

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Revision 1

NOTICE TO APPLICANTS

A GUIDELINE ON

SUMMARY OF PRODUCT CHARACTERISTICS

October 2005

This guideline will be included in The Rules Governing Medicinal Products in the European Union Volume 2C Notice to Applicants

MODULE 1.3 SUMMARY OF PRODUCT CHARACTERISTICS

Article 8(3)(j) of Directive 2001/83/EC and Article 6(1) of Regulation (EC) 726/2004 require that in order to obtain a marketing authorisation, a Summary of Product Characteristics (SPC) in accordance with Article 11 of Directive 2001/83/EC must be included in the application[1]. In accordance with Article 21 of Directive 2001/83/EC, when the marketing authorisation is issued, the Marketing Authorisation Holder shall be informed, by the competent authorities of the Member States concerned, of the SPC as approved by it. For decisions concerning centralised marketing authorisations, according to Article 10 of Regulation (EC) No 726/2004, the final Commission decision with the SPC is addressed and notified to the Marketing Authorisation Holder. Thus, the SPC forms an intrinsic and integral part of the marketing authorisation.

The SPC sets out the agreed position of the medicinal product as distilled during the course of the assessment process. As such the content cannot be changed except with the approval of the originating competent authority.

The SPC is the basis of information for health professionals on how to use the medicinal product safely and effectively. The Package Leaflet (PL) shall be drawn up in accordance with the SPC. The *Guideline on excipients in the label and Package leaflet of medicinal products for human use* is also applicable to the SPC.

It is not in the remit of the SPC to give general advice on the treatment of particular medical conditions. On the other hand specific aspects of the treatment related to use of the medicinal product or its effects should be mentioned.

This guideline provides advice on the principles of presenting information in the SPC. Applicants should maintain the integrity of each section of the document by only including information in each section, which is relevant to the section heading. However, some issues may need to be addressed in more than one section of the SPC and in such situations the individual statements may cross-refer to other sections when these contain relevant additional information.

When a guideline exists for the SPC of a specific therapeutic area (e.g. antibiotics), pharmacological group (e.g. benzodiazepines), or product type (e.g. vaccines), this guideline should be taken into account.

Separate SPCs are required for each pharmaceutical form and strength by the European Commission and certain Member States. Limited references to other strengths or pharmaceutical forms of the same medicinal product may be necessary in an SPC if the dosage regimen is based on the use of several strengths or pharmaceutical forms. For the purposes of giving information to prescribers, the SPCs of different pharmaceutical forms and strengths may be combined for appropriate products within the same range.

SUMMARY OF PRODUCT CHARACTERISTICS: NOTES ON HEADINGS

1 NAME OF THE MEDICINAL PRODUCT

(Invented) name of the medicinal product, strength, pharmaceutical form

In those sections of the SPC in which full information on the name of the medicinal product is specifically required, the name should be followed by both the strength and the pharmaceutical form. However, when otherwise referring to the medicinal product throughout the text, the strength and the pharmaceutical form do not have to be mentioned in the name. The International Non-proprietary Name (INN) or the usual common name of the active substance should be used when referring to properties of the active substance(s) rather than those of the product.

The use of pronouns (e.g. "it") is encouraged whenever possible.

[1] Module 1.3 consists of the SPC.

Strength

The strength should be the relevant quantity for identification and use of the product and should be consistent with the quantity stated in the quantitative composition and in the posology. Different strengths of the same medicinal product should be stated in the same way, e.g. 250 mg, 500 mg, 750 mg. The use of decimal points should be avoided where these can be easily removed (e.g. 250 microgram, not 0.25 mg). However, where a range of medicinal products of the same pharmaceutical form includes strengths of more than one unit (e.g. 250 microgram, 1 mg and 6 mg), it may be more appropriate in certain cases to state the strengths in the same unit for the purpose of comparability (e.g. 0.25 mg, 1 mg and 6 mg). For safety reasons, micrograms and millions (e.g. for units) should always be spelled out in full rather than be abbreviated.

Pharmaceutical form

The pharmaceutical form should be described by the European Pharmacopoeia full standard term using plural form if appropriate (e.g. tablets). If an appropriate standard term does not exist, a new term may be constructed from a combination of standard terms. Should this not be possible, the competent authority should be asked to request a new Standard Term from the European Department for the Quality of Medicines (EDQM) of the Council of Europe. No reference should be made to the route of administration or to the container unless these elements are part of the standard term or where there are identical products, which may be distinguished only by reference to the container.

For the expression of the name and strength of (traditional) herbal medicinal products the declaration should be in accordance with the *Note for Guidance on Quality of Herbal Medicinal Products*.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Full details of the qualitative and quantitative composition in terms of the active substance(s) and constituents of the excipient, knowledge of which is essential for proper administration of the medicinal product should be provided and if appropriate in section 4.3 or 4.4. A standard statement should be included at the end of the section, i.e. 'for full list of excipients, see section 6.1'. See also the *Guideline on the excipients in the label and package leaflet of medicinal products for human use'* as published on the Website of the European Commission in the Notice to Applicants, Volume 3B [http://pharmacos.eudra.org/F2/eudralex/vol-3/home.htm].

If a diluent is part of the medicinal product, information should be included in the relevant sections (usually sections 3, 6.1, 6.5 and 6.6).

Qualitative declaration

The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant, or the European Pharmacopoeial name if that name represents an established name in Europe. If no INN exists, the European Pharmacopoeia name should be used or if the substance is not in the pharmacopoeia, the usual common name should be used. In the absence of a common name, the exact scientific designation should be given. Substances not having an exact scientific designation should be described by a statement on how and from what they were prepared. References to the pharmacopoeial quality should not be included.

Where the medicinal product is a (traditional) herbal medicinal product, the qualitative declaration should be in accordance with the *Note for Guidance on Quality of Herbal Medicinal Products*.

When the medicinal product is a radiopharmaceutical kit, the qualitative declaration should clearly indicate that the radioisotope is not part of the kit.

Quantitative declaration

The quantity of the active substance must be expressed per dosage unit (for metered dose inhalation products, per delivered dose and/or per metered dose), per unit volume, or per unit of weight and must be related to the declaration of strength in section 1.

Salts and hydrates

Where the active substance is present in the form of a salt or hydrate, the quantitative composition should be expressed in terms of the mass (or biological activity in International (or other) units where

appropriate) of the active entity (base, acid or anhydrous material), e.g. '60 mg toremifene (as citrate)' or toremifene citrate equivalent to 60 mg toremifene'.

Where a salt is formed *in situ* during manufacture of the finished product, the quantity of the active entity should be stated, with a reference to the *in situ* formation of the salt.

In the case of established active substances in medicinal products where the strength has traditionally been expressed in the form of a salt or hydrate, the quantitative composition may be declared in terms of the salt or hydrate, e.g. '60 mg diltiazem hydrochloride'. This may also apply when the salt is formed *in situ*.

Esters and pro-drugs

If the active substance is an ester or pro-drug, the quantitative composition should be stated in terms of the quantity of the ester or pro-drug. When the active entity is an active substance of an already approved medicinal product, the quantitative composition should also be stated in terms of the quantity of this active entity.

Oral powders for solution or suspension

The quantity should be stated per unit dose if the product is a single-dose preparation or otherwise per unit dose volume after reconstitution; a reference to the molar concentration may also be appropriate in some cases.

Parenterals excluding powders for reconstitution

For single-dose parenterals, where the total contents of the container are given in a single dose ('total use'), the quantity of active substance(s) should be stated per presentation (e.g. 20 mg etc.) not including any overages or overfill. The quantity per ml and the total labelled volume should also be given.

For single-dose parenterals, where the amount to be given is calculated on the basis of the patient's weight or body surface or other variable ('partial use'), the quantity of active substance(s) should be stated per ml. The quantity per total labelled volume should also be given. Overages or overfills should not be included.

For multi-dose and large volume parenterals, the quantity of active substance(s) should be stated per ml, per 100 ml, per 1000 ml, etc. as appropriate, except for multidose vaccines containing 'n' doses of the same dose. In this case, the strength should be expressed per dose volume. Overages or overfills should not be included.

Where appropriate, e.g. for X-ray contrast media, and parenterals containing inorganic salts, the quantity of active substance(s) should also be indicated in millimoles. For X-ray contrast media with iodine-containing actives substances, the quantity of iodine per ml should be stated in addition to the quantity of the active substance.

Powders for reconstitution prior to parenteral administration

When the product is a powder to be reconstituted prior to administration, the total quantity of active substance in the container should be stated not including overages or overfills, as well as the quantity per ml when reconstituted, unless there are several means of reconstituting, or different quantities used, which result in different final concentrations.

Concentrates

The quantity should be stated as the content per ml in the concentrate and as the total content of the active substance. The content per ml when diluted as recommended should also be included unless the concentrate is to be diluted to within a range of different final concentrations.

Transdermal patches

The following quantitative details should be given: the content of active substance(s) per patch, the mean dose delivered per unit time, and the area of the releasing surface, e.g. 'Each patch contains 750 micrograms of estradiol in a patch size of 10 cm^2, releasing a nominal 25 micrograms of estradiol per 24 hours'.

Multidose solid or semi-solid products

Quantity of active substance should be stated, where possible, per unit dose, otherwise per gram, per 100 g or percentage, as appropriate.

Biological products

In the case of normal immunoglobulins, the IgG subclass distribution should be stated.

In the case of vaccines, the content of active substance per dose unit (e.g. per 0.5 ml) should be stated. Adjuvants, if present, should be stated qualitatively and quantitatively.

The nature of any cellular system(s) used for production, and if relevant the use of recombinant DNA technology, including the use of the expression 'produced in XXX cells <by recombinant DNA technology>'should be mentioned in the SPC, in a pattern as set by the following examples:

- 'produced in human diploid (MRC-5) cells',
- 'produced in *Escherichia coli* cells by recombinant DNA technology',
- 'produced in chick-embryo cells' and
- 'derived from human plasma donors'.

Herbal medicinal products

The quantitative declaration should be in accordance with the *Note for Guidance on Quality of Herbal Medicinal Products.*

3 PHARMACEUTICAL FORM

The pharmaceutical form should be described by the European Pharmacopoeia full standard term (see section 1). The term used in this section should be the same as the term used in section 1. However, where a European Pharmacopoeia short standard term is used on small immediate packaging material, the short term should be added in brackets in this section.

It is recommended that a visual description of the appearance of the product (colour, markings, etc.) is given, in a separate paragraph to the standard term, including information on pH and osmolarity as required e.g.

'*Tablet*

White, circular flat bevelled-edge tablets marked '100' on one side'

In case of tablets designed with a score line, information should be given whether or not reproducible dividing of the tablets has been shown. e.g. 'the scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses', 'the tablet can be divided into equal halves'.

In case of products to be reconstituted before use, the appearance before reconstitution should be stated in this section. Appearance of the product after reconstitution should be stated in section 4.2.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The indication(s) should be stated clearly and concisely and should define the target disease or condition distinguishing between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and diagnostic indication. When appropriate it should define the target population especially when restrictions to the patient populations apply.

Study endpoints should not normally be included unless such mention is specified as being appropriate for the indication in CHMP Notes for Guidance or Points to Consider Documents. The objective of a prevention indication may be mentioned in general terms only. This should also be done for the target population.

Where results from subsequent studies provide further definition or information on a licensed indication, such information, provided it does not itself constitute a new indication, may be considered for inclusion in section 5.1.

Mandatory conditions of product usage not covered more appropriately in other parts of the SPC may also be included when relevant, e.g. concomitant dietary measures, lifestyle changes, or other therapy.

When the product is indicated in a specific age group such as children/adolescents, the indication should state the age limit e.g. 'X is indicated in <children> <adolescents> from the age of X <months><years >'.

4.2 Posology and method of administration

In case of restricted medical prescription, this section should be started by specifying the conditions.

The dosage has to be clearly specified for each method/route of administration and for each indication.

Where appropriate, a reference to official recommendations should be made (e.g. for primary vaccination and antibiotics as well as for booster dose).

Specify dose recommendations per dose interval in an appropriate way (e.g. mg, mg/kg, mg/m^2) for each age category where appropriate (specify age ranges), i.e. children as specified (see also *Note for Guidance on Clinical Investigation of Medicinal Products in Children (CPMP/EWP/462/95)*, adults, and the elderly.

Short relevant instruction for correct administration/use should also be given here. In section 6.6 'Special precautions for disposal of a used medicinal product and other handling of the product' information should be placed for instructions for preparation and/or reconstitution or in section 12 and cross-referenced here.

Where appropriate, the following points should be addressed:

- the maximum recommended single, daily and/or total dose,
- the need for dose titration,
- the normal duration of use and any restrictions on duration and, if relevant, the need for tapering off, or advice on discontinuation,
- advice on action to be taken if one or more dose(s) is (are) missed,
- advice on preventive measures to avoid certain adverse drug reactions (e.g. administration of antiemetics) with cross-reference to section 4.4,
- the intake of the product in relation to food intake,
- advice regarding repeat use, with any information on intervals to be observed between courses of treatment, as appropriate, and
- interactions requiring specific dose adjustments with cross-reference to other appropriate sections of the SPC (e.g. 4.4, 4.5, 4.8, 5.1, 5.2).

Where relevant to the particular product, an entry such as the following should appear 'The potency of this medicinal product is expressed in <invented name> units. These units are not interchangeable with the units used to express the potency of other <active substance name> preparations'.

Additional information on special populations

Available relevant information on special populations such as renal/hepatic impairment, geriatric or paediatric patients should be presented here.

Renal/hepatic impairment

Dosage adjustments in specific patient groups should be stated e.g. regarding:

- renal insufficiency; the dose recommendation should relate as precisely as possible to the cut-off values for biochemical markers of renal impairment clinical studies and to the results of these studies.

- liver disease, specified according to the patients included in studies, for instance 'alcohol-related cirrhosis' and the definitions used in the studies, for instance Child-Pugh score/grade of the patients, and
- other concomitant diseases.

Advice relevant for dosage adjustment e.g. from monitoring of clinical symptoms and signs, and/or laboratory investigations, including medicinal product concentrations should be mentioned when appropriate.

Paediatric population

When the medicinal product is to be used in children, a specific sub-section 'paediatric patients' should be identified.

Information should be given for the different sub-populations of children i.e. according to the ICH guideline E11.

The age limits should reflect the assessment of the available documentation and relate to age intervals where a different dosing is recommended. The information given should relate to ages for which satisfactory efficacy and safety have been shown. If necessary in preterm and term newborns, information should be written taking into account the gestational age or the post-conception age.

The dose schedule studied and found satisfactory should be given in this section. Taking account of available paediatric formulations, the dose may be related to weight or body surface area depending on what has been found optimal, e.g. children age 2-4 years, 1 mg/bodyweight b.i.d. for 1 week (up to the adult dose).

If a paediatric indication has not been approved, the following text is suggested under a subheading 'paediatric patients':

a. X is not recommended for use in children <above><below> age Y due to <a lack of ><insufficient> data on safety and/or efficacy (the age should be specified)' (with a possible cross-reference to section 5.1 and/or 5.2)

b. The experience in children is limited. There is no experience in children. See sections 4.4 and 5.2.

c. 'Use in children – there is no relevant indication for use of <Invented name> in children' (when the indication is not relevant to this population).

d. 'X is contraindicated in children' (cross-reference to section 4.3)

If the product has not been studied in the paediatric population or if there are insufficient data on which to base an approval for paediatric use, it should be stated that the medicinal product is not recommended in the paediatric age group until further data become available. If available, additional information on the reason for the advice, and on the use in the paediatric age groups, can be included in sections 4.4, 5.1 or 5.3, as appropriate, together with a cross reference from this section.

Any such statement(s) regarding paediatric age groups should be transparent and reflect the available data.

In exceptional cases where the "adult formulation" of a medicinal product includes an indication and a posology for use in children, or includes, at least, posology recommendations for use in children, and where no adequate paediatric formulation can be developed based on duly justified scientific grounds (i.e. where the extemporaneous preparation of a formulation for paediatric use from the adult one is necessary), relevant instructions for the extemporaneous preparation shall be included in section 6.6 with a cross-reference in section 4.2. Such information shall be provided by the Marketing Authorisation Holder with a view to improve the quality, safety and efficacy of such extemporaneous preparations for use in children.

4.3 Contraindications

Situations where the medicinal product must not be given for safety reasons, i.e. contraindications, are the subject of this section. Such circumstances could include particular clinical diagnosis, concomitant

diseases, demographic factors (e.g. gender, age) or predispositions (e.g. metabolic or immunological factors, prior adverse reactions to the medicine or class of medicines). The situations must be unambiguously, comprehensively and clearly outlined.

Other medicines or classes of medicine, which must not be used concomitantly or consecutively should be stated, either based on data or strong theoretical reasons. If applicable a cross-reference to section 4.5 should be given.

In general, patient populations not studied in the clinical trial programme should be mentioned in section 4.4 and not in this section unless a safety issue can be predicted (e.g. use of renally cleared substances with narrow therapeutic margin in renal failure patients). If, however, patients have been excluded from studies as being contraindicated on serious grounds of safety, they should be mentioned in this section. If applicable a cross-reference to section 4.5 should be given.

Only if pregnancy is strictly contraindicated, should it be mentioned here. In section 4.6, a cross-reference should be given and further information about the background be provided.

Hypersensitivity to any of the excipients or residues from the manufacturing process should be included, as well as any contraindication arising from the presence of certain excipients (see *Guideline on excipients in the label and package leaflet of medicinal products for Human Use*).

For herbal medicinal products, hypersensitivity extended to other plants of the same family or to other parts of the same plant should be labelled as a contraindication, where applicable.

4.4 Special warnings and precautions for use

The order of warnings and precautions should be determined by the importance of the safety information provided.

The exact content of this section will be different for each product and the therapeutic conditions it is intended to treat. It is however suggested that the following items should be included where relevant to the specific product. Patient groups in which use of the medicinal product is contraindicated should be mentioned in section 4.3 only and not to be repeated here. The below mentioned particulars should be described:

- The conditions under which use of the medicinal product could be acceptable, provided that special conditions for use are fulfilled.
- Special patient groups, such as elderly and children, that are likely to experience product or class related adverse reactions (ADRs) occurring under normal conditions of use e.g. specified age groups, patients with renal, hepatic impairment (including the degree of impairment, such as mild, moderate or severe) or cardiac failure (including the NYHA classification).
- Circumstances where all patients are at risk of a specified adverse reaction, but the incidence or severity of the reaction differs in particular populations.
- Serious adverse reactions to which the prescriber needs to be alert, the situations in which these may occur and the action that may be required, e.g. emergency resuscitation.
- When the outcome of an adverse reaction is particularly serious and/or frequent, this could be emphasised by presenting the statement at the top of this section.
- If there are particular risks associated with starting the medicinal product (e.g. first dose effects) or stopping it (e.g. rebound, withdrawal effects), these should be mentioned in this section, together with the action required for prevention.
- Any measures which can be taken to identify patients at risk and prevent the occurrence, or detect early the onset or worsening of noxious conditions. If there is a need for awareness of symptoms or signs representing early warning of a serious ADR, a statement should be included. Any need for specific clinical or laboratory monitoring should be stated. If dose reduction is recommended in such circumstances or conditions, this should be included in section 4.2 and cross-referenced here.

- Clinically relevant interactions where in general the use of the combination should be avoided should be mentioned here with a cross-reference to section 4.5.
- Any warnings necessary for excipients or residues from the manufacturing process.

In exceptional cases, especially important safety information may be included in bold type within a box.

Any adverse reactions described in this section or known to result from conditions mentioned here must also be included in section 4.8.

In case of immunologicals, any special precautions to be taken by persons handling such products and administering them to patients, together with any precautions to be taken by the patient.

Specific interaction with biological test should be mentioned when appropriate, e.g. Coombs test and Beta-lactams.

Descriptions of warnings and precautions regarding pregnancy and lactation, ability to drive and use machines, and other aspects of interactions should be dealt with in sections 4.6, 4.7 and 4.5, respectively.

4.5 Interaction with other medicinal products and other forms of interaction

This section should provide information on the potential for clinically relevant interactions based on the pharmacodynamic properties and *in vivo* pharmacokinetic studies of the medicinal product, with a particular emphasis on the interactions, which result in a recommendation regarding the use of this medicinal product This includes *in vivo* interaction results which are important for extrapolating an effect on a marker ('probe') substance to other medicinal products having the same pharmacokinetic property as the marker.'

Interactions affecting the use of this medicinal product should be given first, followed by those interactions resulting in clinically relevant changes on the use of others.

Interactions referred to in other sections of the SPC should be described here and cross-referenced from other sections.

The order of presentation should be contraindicated combinations, those where concomitant use is not recommended, followed by others.

The following information should be given for each clinically relevant interaction:

a. Recommendations: these might be
   - contraindications of concomitant use (cross-refer to section 4.3),
   - concomitant use not recommended (cross-refer to section 4.4), and
   - precautions including dose adjustment (cross-refer to sections 4.2 and 4.4), mentioning specific situations where these may be required; for the actual dose recommendation, cross-refer to section 4.2.

b. Any clinical manifestations and effects on plasma levels and AUC of parent compounds or active metabolites and/or on laboratory parameters.

c. Mechanism, if known.

Interactions not studied *in vivo* but predicted from *in vitro* studies or deducible from other situations or studies should be described if they result in a change in the use of the medicinal product, cross-referring to sections 4.2 or 4.4.

This section should mention the duration of interaction when a medicinal product with clinically important interaction (e.g., enzyme inhibitor or inducer) is discontinued. Adjustment of dosing may be required as a result. The implication for the need for a washout period when using medicines consecutively should also be mentioned.

Information on other relevant interactions such as with herbal medicinal products, food or, pharmacologically active substances not used for medical purpose, should also be given. With regard

to pharmacodynamic effects where there is a possibility of a clinically relevant potentiation or a harmful additive effect, this should be stated.

Results demonstrating an absence of interaction should only be mentioned here if this is of likely major interest to the prescriber.

If no interaction studies have been performed, this should be clearly stated.

Additional information on special populations

If there are patient groups in which the impact of an interaction is more severe, or the magnitude of an interaction is expected to be larger e.g., patients with decreased renal function (in case the parallel pathway is renal excretion), paediatric patients, elderly etc, this information should be given here. If the medicinal product is indicated in children and interaction studies have been performed in adults only, this information should be given together with recommendations on concomitant use.

Paediatric population

Information specific to a special age group should be given here.

If interactions exist that are specific to children this information could be given under a subheading 'paediatric patients'. General effects of a drug on enzymes are probably the same in adults and children. However, the resulting exposure and clinical consequences of a pharmacokinetic interaction can differ between adults and children, Therefore, if the interaction studies have been performed in adults, the statement 'Interaction studies have only been performed in adults' should be included if considered relevant to the prescriber. This is especially important if any specific dose recommendations are made. The same also applies to pharmacodynamic drug interactions.

In cases where there is an interaction with food leading to a recommendation on co-administration with a meal or specific food, it should, if possible, be noted whether this information is relevant for children (especially newborns and infants) whose diet may be totally different (100 % milk in newborns versus maybe 0 % in adults) compared to the study setting leading to the recommendation.

If no interaction studies have been performed, this should be clearly stated.

4.6 Pregnancy and lactation

General recommendation

'Contra-indication in pregnancy' should be supported by human data (teratogenicity or fetotoxicity) or by strong nonclinical data. When a contra-indication in pregnancy or lactation is made, this should be included in section 4.3.

Efforts should be made by the Marketing Authorisation Holder to provide the reasons for recommendations for use in pregnant or lactating women, and in women of childbearing potential.

The following should be mentioned:

Women of childbearing potential / Contraception

Recommendations on the use of the medicinal product in women of childbearing potential should be given when appropriate including pregnancy test, contraception. Where an effective contraception is required for patients or partners of patients during treatment and for a defined period after ending treatment, the rationale should be included in this section (see Annex 1).

Pregnancy

With respect to nonclinical data,

- only conclusions of the reproductive studies should be included in this section. The species in which the product has been tested can be specified if they are different to the species recommended by a guideline. Further details should be provided in section 5.3.
- the conclusions of nonclinical toxicity studies are not necessary and should not be mentioned if a product is known to be teratogenic in humans or if it is known to be safe in humans.

With respect to clinical data,

- the section should include comprehensive information on relevant adverse events reported in the embryo, the fetus, neonates and pregnant women, when appropriate. The frequency of such events (for example the frequency of birth defects) may be specified when available.
- the section should specify the extent of the human experience if no adverse events have been reported in pregnancy (no experience, limited experience).

Consequently, the paragraph should include:

a) Clinical data from human experience in pregnancy with the frequency when appropriate.

b) Conclusions from developmental studies, which are relevant for the assessment of the risk, associated with exposure during pregnancy. Only malformative, fetotoxic and neonatal effects should be mentioned in this paragraph. Further details should be included in section 5.3 when appropriate.

c) Recommendations on the use of the medicinal product during the different periods of gestation. A sentence should provide the reason(s) of these recommendations.

d) Recommendations for the management of exposure during pregnancy when appropriate (including relevant specific monitoring such as fetal ultrasound, specific biological or clinical surveillance of the neonate).

Cross-references can be included in sections 4.3, 4.4 and 4.8, as appropriate.

Examples of the wording of this section are given in Annex 1.

Lactation

If available, clinical data should be mentioned including the conclusions of the studies on the transfer of the active substance and/or its metabolite(s) into human milk (positive/negative excretion, milk/serum ratio). Further details should be included in section 5.2. Information on adverse events in nursing neonates should be included if available.

Recommendations should be given to stop or continue breast-feeding and/or to stop or continue the treatment in case where treatment or breastfeeding discontinuation is recommended, the reason should be provided.

Conclusion on animal studies on the transfer of the active substance and/or its metabolite(s) into milk should be given only if no human data are available.

Example wordings to be used in this section are appended in Annex 3.

Fertility

No wording on fertility is necessary if there is no (human or nonclinical) fertility data available.

The main information on the possible effects of the medicinal product on male and female fertility must be included in section here.

The paragraph should include:

a) Clinical data if available.

b) Relevant conclusions from nonclinical toxicity studies if available (to be discussed with toxicologists, in particular with regard to predictive value). Further details should be included in section 5.3.

c) Recommendations for the use of the medicinal product when pregnancy is planned but fertility might be affected by treatment.

If necessary, cross-references can be included in section 4.3, as appropriate.

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic profile, reported Adverse Reactions and/or specific studies on a relevant target population addressing the performance related to driving or using machines, specify whether the medicinal product has a) no or negligible influence b) minor or moderate influence or c) major influence on these abilities. Effects of the disease itself on these abilities should not be discussed.

For situations b and c, special warnings/precautions for use should be mentioned.

4.8 Undesirable effects

This section should provide comprehensive information based on all adverse reactions (ADRs) from clinical trials, post-marketing studies or spontaneous reports attributed to the medicinal product with at least reasonable suspicion and on a best-evidence assessment of all observed adverse events and all facts relevant to the assessment of causality, severity and frequency. In this context, all adverse reactions should be included in the SPC if they are at least possibly causally related, based for example on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual reports. Adverse events, without at least a suspected causal relationship, should not be listed in the SPC.

It is important that the whole section should be worded in concise and specific language and it should not include information such as claims regarding the absence of specific adverse reactions, comparative frequency statements other than as described below, or statements of general good tolerability. Statements on lack of proof of causal association are not helpful and should not be included.

In order to provide clear and readily accessed information, it should be structured according to the following recommendations:

a. A general description will be necessary for most products. It should state what are the most serious and/or most frequently occurring ADRs. It should be placed before the detailed and specific information presented in the table(s) (see below b.). This description, which should be as brief as possible, should start by providing an estimate of the overall percentage of treated patients expected to experience adverse reactions. This information must be consistent with the figures presented and must not contain general statements such as 'well tolerated', 'ADRs are normally rare' etc. Examples of acceptable statements (addressing overall and organ specific frequency related to the target population) are given below:

   'Approximately 15% of patients can be expected to experience adverse reactions. These are mainly dose dependent and due to the pharmacologic effects of the medicinal product.'
   or

   'ADR are rare (<1/1,000). At the beginning of therapy, epigastric pain, nausea, diarrhoea, headache or vertigo may occur: these reactions are usually mild and disappear within a few days even if treatment is continued (see also section (c) below).'

   'The most commonly reported ADRs are dizziness and headache, both occurring in approximately 6% of patients.'

   'About 30% of treated patients experience adverse reactions: they usually occur within the first three months after the start of therapy. Dose-related ADR, such as gastrointestinal reactions and headache, can sometimes be alleviated by reducing the dose (see also section (c) below.'

b. A single table of adverse reactions according to the MedDRA system organ class. The system organ classes should be presented in the order shown in Annex 2. Adverse reactions descriptions should be based on the most suitable representation within the MedDRA terminology. This will usually be at the Preferred Term Level, although there may be instances where the use of Lowest Term Level or exceptionally group terms, such as High Level Terms may be appropriate. As a general rule, any ADR should be assigned to the most relevant SOC related to the target organ. For example, 'Liver function test abnormal' should be assigned to

the SOC 'Hepatobiliary disorders' rather than to the SOC 'Investigations'. Within each system organ class, the ADRs should be ranked under headings of frequency, most frequent reactions first, using the following convention:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated form the available data).

The names used to describe each of the frequency groupings should follow standard terms established in each official language. Within each frequency grouping, adverse reactions should be presented in order of decreasing seriousness.

The expressions isolated/single cases/reports should not be used. If for a specific ADR a frequency cannot be estimated or a frequency category not be chosen an additional category frequency 'not known' may be added.

The choice of the frequency category to which any ADR will be assigned is based on frequency data derived from a study (clinical trial or epidemiological study) designed in such a way that when a specific adverse event had been reported in a patient it would have been detected within the defined observation period, reported, and assessed at least as a 'possible' reaction. This generally requires the use of adequate data collection and causality evaluation methods. In this situation, it is possible to calculate a point estimate of the crude incidence rate and its confidence interval, using standard statistical methods and taking into account the nature of the data (numerator, denominator, time dimension). The point estimate should be used to allocate an ADR to a frequency category.

If the choice of the frequency category is based on more than one suitable study the category representing the highest frequency should be chosen unless application of a more specific method for detection of the ADR has been applied and thus resulted in an estimate of clearly higher validity, e.g. an integrated analysis across the suitable studies. The category to be chosen for each ADR should not be representing differences (calculated against placebo or other comparator) but crude incidence rates.

The frequencies based on reporting rates from a spontaneous reporting system should not be used for choosing a frequency category in any situation. If it is decided that an ADR detected by spontaneous reports should be included, each adequately designed study where this ADR could have been detected should be reviewed. If no valid estimate of the incidence rate can be derived from these studies it has to be classified as 'Not known'. When various galenical/pharmaceutical formulations of a medicinal product are available, appropriate clinical trial data for suitable formulations may be combined for the assessment of frequency categories (e.g. various oral or enteral formulations). This would aim to obtaining more robust results. In the case of different modes of application (e.g. enteral versus parenteral versus inhalation etc.), these should be dealt with separately.

A tabulation of ADR frequency estimates from clinical trials, stated as a fraction expressed per 1,000 exposed patients (incidence rates, related confidence intervals), which do not serve the purpose of assignment to the defined frequency categories may only be included when it is of particular relevance to the patient and/or prescriber to be informed of certain risks and related frequency estimates. In these cases it is preferable that the data should be based on pooled study results or large targeted studies performed under actual market conditions.

When data come from a placebo-controlled trial or a study with a non-exposed group and the rate difference attributed to the medicinal product is smaller than the baseline incidence rate, and if the ADR is considered important, the background incidence may be provided in a footnote, or results may be presented as an added column or in a separate table.

In these exceptional instances where more precise frequencies are stated, the figures should be annotated with a footnote describing how the data were obtained. The methods used to derive the figures will vary but must be appropriate to the circumstances. The annotation might read, for example:

'Excess incidence compared with placebo in pooled data from clinical trials involving x patients taking the medicinal product and y patients taking placebo, where the placebo incidence was z',

'Incidence of the suspected adverse reaction in an observational post study in x patients'.

If there are only a few adverse reactions in total in this section, tabulation by system organ class may be unnecessary.

Where additional details about an adverse reaction are described in section c), the reaction concerned should be highlighted, for example with an asterisk, and 'see section c)' should be included as a footnote.

c. This section should include information characterising individual serious and/or frequently occurring adverse reactions, or those where there have been reports of particularly severe cases. The information may describe for example reversibility or time of onset the severity, duration of reaction, mechanism of the reaction (if of clinical relevance), or dose relationship. Mention should be made here of any differences between different dosage forms in respect of adverse reactions. In the case of combination products, a statement should be included in this section pointing out which particular adverse reactions are usually attributable to which component of the combination, where known.

Measures to be taken to avoid specific adverse reactions or actions to be taken if specific reactions occur (if of particular importance) should be mentioned under section 4.4 and cross-referenced here.

Any adverse reactions resulting directly from an interaction should be mentioned here and cross-referenced to section 4.5.

d. This section should include adverse reactions, which apply to the therapeutic chemical or pharmacological class-adverse reactions of very low frequency or with delayed onset of symptoms which may not have been observed yet in relation to the product, but which are generally accepted as being attributable to other compounds in the class. The fact that this is a class attribution should be mentioned.

Any undesirable event warnings necessary for excipients or residues from the manufacturing process should be included.

Additional information on special populations

Information specifically observed in other special populations such as elderly patients, patients with renal insufficiency, patients with hepatic insufficiencies, other concomitant diseases etc.

Paediatric population

If some undesirable effects are specifically observed in children or if altered frequencies of undesirable effects are observed, this information should be given in a subsection entitled 'paediatric patients'. If possible, the information could be divided into ICH E11 age groups. If a similar safety profile is expected in children as in adults this could be stated. For existing products it is possible that the requirements cannot be fulfilled because the necessary information is not available. In other cases, the recommendations apply.

4.9 Overdose

Describe acute symptoms and signs and potential sequelae of different dose levels of the medicinal product based on accidental mistakes and suicide attempts by patients.

Describe management of overdose in man, e.g. in relation to specific agonists/antagonists or methods to increase elimination of the medicinal product e.g. dialysis.

Additional information on special populations

Information specifically observed in other special populations such as elderly patients, patients with renal insufficiency, patients with hepatic insufficiencies, other concomitant diseases etc.

Paediatric population

If there are specific paediatric considerations, there should be a sub-section entitled 'paediatric patients'.

It might be useful to have a special mentioning for those medicinal products which can cause a fatal poisoning in the special risk group of young children (for instance a bodyweight of 10 kg could be used as the limit) if just a single tablet is ingested. This is a limited special group of medicines, which should be kept with extra care.

5. PHARMACOLOGICAL PROPERTIES

Sections 5.1 – 5.3 should normally mention information, which is relevant to the prescriber *and to other health-care professionals,* taking into account the approved therapeutic indication(s) and the potential adverse drug reactions. Statements should be brief and precise.

5.1 Pharmacodynamic properties

Describe:

- Pharmacotherapeutic group (ATC code). If an ATC code is not yet available, this should be mentioned as 'not yet assigned'.
- Mechanism of action (if known)
- Pharmacodynamic effects.
- Clinical efficacy and safety

It may be appropriate to provide limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified end points or clinical outcomes in the major trials, giving the main characteristics of the patient population. Such information on clinical trials should be concise, clear, relevant and balanced and summarise evidence from relevant studies supporting the indication.

If information from subgroup or post hoc analyses that is considered clinically relevant is presented and identified as such, this should be in a balanced way, which reflects the limited robustness of both positive and negative secondary observations. The magnitude of effects should be described using relative and absolute figures.

[For products approved under 'conditional approval' in the centralised procedure, include the following statement:]

<This medicinal product has been authorised under a so-called 'conditional approval' scheme.

This means that further evidence on this medicinal product is awaited.

The European Medicines Agency (EMEA) will review new information on the product every year and this SPC will be updated as necessary.>

[For products approved under 'exceptional circumstances', include the following statement:]

<This medicinal product has been authorised under 'Exceptional Circumstances'.

This means that <due to the rarity of the disease> <for scientific reasons> <for ethical reasons> it has not been possible to obtain complete information on this medicinal product.

The {name of Agency} will review any new information which may become available every year and this SPC will be updated as necessary.>

5.2 Pharmacokinetic properties

Pharmacokinetic properties of the active substance(s) relevant for the advised dose, strength and the pharmaceutical formulation marketed should be given in this section. If these are not available, results obtained with other administration routes, other pharmaceutical forms or doses can be given as alternative.

Basic primary pharmacokinetic parameters, for instance bioavailability, clearance and half-life, should be given as mean values with a measure of variability.

Pharmacokinetics items, which could be included in this section when relevant, are given below.

a. General introduction, information about whether the medicinal product is a pro-drug or whether there are active metabolites, chirality, solubility etc.

b. General characteristics of the active substance(s) after administration of the medicinal product formulation to be marketed.

- **Absorption:** complete or incomplete absorption; absolute and/or relative bioavailability; first pass effect; Tmax; the influence of food; in case of locally applied medicinal product the systemic bioavailability.
- **Distribution:** plasma protein binding; volume of distribution; tissue and/or plasma concentrations; pronounced multi-compartment behaviour.
- **Biotransformation:** degree of metabolism; which metabolites; activity of metabolites; enzymes involved in metabolism; site of metabolism; results from in vitro interaction studies that indicate whether the new compound can induce/inhibit metabolic enzymes.
- **Elimination:** elimination half-lives, the total clearance; inter and/or intra-subject variability in total clearance; excretion routes of the unchanged substance and the metabolites.
- **Linearity/non-linearity:** linearity/non-linearity of the pharmacokinetics of the new compound with respect to dose and/or time; if the pharmacokinetics are nonlinear with respect to dose and/or time, the underlying reason for the non-linearity should be presented.

Additional relevant information should be included here.

c. Characteristics in patients

- Variations with respect to factors such as age, gender, smoking status, polymorphic metabolism and concomitant pathological situations such as renal failure, hepatic insufficiency, including degree of impairment. If this influence on the pharmacokinetics is considered to be clinically relevant, it should be described here in quantitative terms (cross-referral to 4.2 when applicable).

d. Pharmacokinetic/pharmacodynamic relationship(s)

- Relationship between dose/concentration/pharmacokinetic parameter and effect (either true endpoint, validated surrogate endpoint or a side effect).
- Contribution (if any) of metabolite(s) to the effect.

5.3 Preclinical safety data

Information should be given on any findings in the preclinical testing which could be of relevance for the prescriber, in recognising the safety profile of the medicinal product used for the authorised indication(s), and which is not already included in other relevant sections of the SPC.

During the development of a new medicinal product, a variety of preclinical studies will be performed. These are assessed by the competent authority when evaluating the application. If the results of the studies do not add to the information needed by the prescriber, then the results (either positive or negative) need not be repeated in the SPC.

The findings of the non-clinical testing should be described in brief and qualitative statements as outlined in the following example statements:

- Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

- Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
- Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows.

Conclusions on the environmental risk assessment on the product should be included where relevant, with reference to section 6.6.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

A list should be given of the excipients, expressed qualitatively only. All excipients, which are present in the product, should be included, even those present in small amounts, such as printing inks. Further details on the excipients to be declared may be found in the section on definitions and examples in the *Guideline on the Excipients in the Label and Package Leaflet of Medicinal Products for Human Use.* For transdermal patches, all ingredients of the patch (including the adhesive, release liner and backing film) should be mentioned.

The active substance itself, residues of substances used during manufacture of the finished product (for example, solvents, head-space gases or antibiotics in vaccine manufacture), lubricants for pre-filled syringes and constituents of capsule shells for inhalation powders not intended to be taken should not be included.

However, certain residues such as residues of antibiotic or other antimicrobial agents used in production that are known allergens with a potential for inducing undesirable effects should be mentioned in section 4.3.

Excipients should be referred to by their recommended INN if existing, accompanied by the salt or hydrate form if relevant or by their European Pharmacopoeia name. If an excipient has neither an INN nor European Pharmacopoeia.. name, it should be described by its usual common name. References to the pharmacopoeial quality should not be included. E numbers should be given where they exist and when the excipient is listed in the *Guideline on the excipients in the label and package leaflet of medicinal products for human use* (as having recognised action or effect), along with the common name of the excipient.

The ingredients in excipient mixtures should be listed individually. In cases where the full composition of a flavour or fragrance is not known to the applicant, they may be declared in general terms (e.g. 'orange flavour', 'citrus perfume'). However, any of the components, which are known, or which have a recognised action or effect must be included.

Ingredients that may or may not be added for the pH adjustment should be followed by the parenthesis '(for pH-adjustment)'

Invented names or general descriptive names such as 'printing ink' should not be used in place of the common name of an ingredient or of a mixture of ingredients but may be used in conjunction with the name(s) of the ingredient(s), so long as it is clear which ingredients are described by the name.

Chemically modified excipients should be declared in such a way as to avoid confusion with the unmodified excipients, e.g. 'pregelatinised starch'.

For clarity, it is recommended that each excipient be listed on a separate line. It can be useful to list excipients according to the different parts of the product, e.g. tablet core/coat, capsule contents/shells, etc. For products that are presented in more than one container or in dual-chamber containers, the excipients should be listed per container or per chamber.

Abbreviations for excipients should not be used. However, where justified for space considerations, abbreviations for excipient names may appear on the labelling, on condition that these abbreviations are designated in section 6.1.

8. Well-conducted epidemiological studies indicate no adverse effects of {Generic name} on pregnancy or on the health of the foetus/newborn child.

   {Trade name} can be used during pregnancy.

9. In case of interaction with oral contraceptives information should also be given in section 4.5.

   {Generic name} adversely interacts with oral contraceptives (OCs). Therefore, an alternative, effective and safe method of contraception should be used during (and up to x weeks after) treatment.

   or

   The concomitant medication [Generic name} adversely interacts with oral contraceptives {OCs). Therefore an alternative, effective and safe method of contraception should be used during (and up to x weeks after) treatment.

10. In case of male-mediated effects on pregnancy outcome information should also be given in section 4.4.

    Both sexually active men and women should use effective methods of contraception during (and up to x weeks after) treatment

ANNEX 2

THE MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES TERMINOLOGY (MedDRA)

All ADRs should be grouped according to the MedDRA system organ classes (SOC). As a general rule, MedDRA terms should be classified according to the most relevant SOC related to the target organ.

A pragmatic approach to the location of terms should be taken in order to make the identification of adverse reactions simpler and clinically appropriate for the reader. For example, it may be helpful on some occasions – solely in the context of the SPC - to use secondary SOC locations of some MedDRA Preferred Terms (PT), or sometimes to use locations that do not strictly accord with the MedDRA architecture. For example, if the terms 'Liver function test abnormal', 'Hepatitis' and 'Hepatic encephalopathy' are to be included in an SPC, it would be acceptable to include them all under the 'Hepato-biliary SOC' instead of distributing the reactions among the 'Hepato-biliary disorders', 'Nervous system disorders' and 'Investigations System Organ Classes' as dictated by their primary location in MedDRA.

SOC LIST - INTERNATIONALLY AGREED ORDER

- Infections and infestations
- Neoplasms benign and malignant (including cysts and polyps)
- Blood and the lymphatic system disorders
- Immune system disorders
- Endocrine disorders
- Metabolism and nutrition disorders
- Psychiatric disorders
- Nervous system disorders
- Eye disorders
- Ear and labyrinth disorders
- Cardiac disorders
- Vascular disorders
- Respiratory, thoracic and mediastinal disorders
- Gastrointestinal disorders
- Hepato-biliary disorders
- Skin and subcutaneous tissue disorders
- Musculoskeletal, connective tissue and bone disorders
- Renal and urinary disorders
- Pregnancy, puerperium and perinatal conditions
- Reproductive system and breast disorders
- Congenital and familial/genetic disorders
- General disorders and administration site conditions
- Investigations
- Injury and poisoning
- Surgical and medical procedures
- Social circumstances

ADR descriptions should be based on the most suitable representation within the MedDRA terminology. This will usually be at the PT level, although there may be instances where the use of Lowest Level Terms (LLT) or group terms, such as high-level terms (HLT) may be appropriate. It is acceptable to adapt the names of the MedDRA group terms if this makes their meaning more transparent to the reader of the SPC; e.g. the HLT *Genitourinary tract disorders NEC*, if otherwise appropriate for the SPC under consideration, could be presented without the suffix 'NEC'. The use of the suffixes NEC and NOS are not appropriate for inclusion in the SPC. The adverse reaction term should be expressed in natural word order, e.g. 'Interstitial pneumonia' in preference to 'Pneumonia interstitial'. It may be appropriate to modify MedDRA terms in other ways in the interests of comprehensibility. The most widely recognised term for a particular condition should be used, e.g. the

10. No effects on the suckling child are anticipated. {Invented name} can be used during breast-feeding. *E.g. most vitamin and mineral formulations.*

EXHIBIT 32

PhRMA

Delivering on the Promise of Pharmaceutical Innovation: The Need to Maintain Strong and Predictable Intellectual Property Rights

WHITE PAPER

on

The Intersection of Intellectual Property and Antitrust Law
in the
Pharmaceutical Industry

Submitted To
Federal Trade Commission
and the
Department of Justice – Antitrust Division

April 22, 2002

Pharmaceutical Research and Manufacturers of America
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Delivering on the Promise of Pharmaceutical Innovation: The Need to Maintain Strong and Predictable Intellectual Property Rights

based pharmaceutical companies. For each drug approved by FDA, a company typically screens between 5,000 and 10,000 compounds. [22]

From 1998-2000, research-based pharmaceutical companies allocated an average of 79.7% of their R&D expenditures to the research and evaluation of new drug products.[23] The remaining 20.3% is devoted to research into significant improvements and/or modifications to existing products.[24] Such significant adjustments can include enhanced efficacy, improved dosage and delivery forms and patient-tailored therapies. The clinical value of research into improvements and incremental innovations is high and should not be undermined. (See **Part III.**)

C. Strong Intellectual Property Protection is Essential to a Vital Innovative Pharmaceutical Industry.

The discovery and development of new medicines is an expensive and time-consuming process. As with most inventors, particularly those who cannot rely on trade secret protections, pharmaceutical companies rely on patent protection to provide an opportunity to recover their R&D investments. Because of the extraordinary costs and risks of drug development, and the relative ease and extremely low absolute and relative costs of generic copies, strong intellectual property protection is *the* key to a viable, innovative pharmaceutical industry. Without these protections innovation would stop and with it all meaningful competition for new cures.

The U.S. pharmaceutical industry leads the world in pharmaceutical research and development. However, the costs of developing a new drug are large and increasing. In fact, new drug development costs have skyrocketed. The Tufts Center announced on November 30, 2001, that the average cost to develop a new prescription drug is $802 million (in 2000 dollars),[25] a figure that includes costs of R&D failures and opportunity costs. Similarly, Boston Consulting Group modeling has found the average costs per drug to be approximately $818 million.

As of 1993, the Office of Technology Assessment estimated that the fully capitalized cost of developing a new pharmaceutical was $359 million in pretax 1990 dollars for drugs that first entered human testing in the period 1970-1982.[26] In 1996, because of the increasing complexity

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[22] *Id.*

[23] PhRMA, 2002 Industry Profile, table 4, at 78.

[24] *Id.*

[25] Press Release, Tufts University, Tufts Center for the Study of Drug Development Pegs Cost of New Prescription Medicine at $802 Million (Nov. 30, 2001), *available at* http://www.tufts.edu/med/csdd ; Backrounder, Tufts Center for the Study of Drug Development, A Methodology for Counting Costs for Pharmaceutical R & D (Nov. 30, 2001), *available at* http://www.tufts.edu/med/csdd

[26] Congress of the United States, Office of Technology Assessment, OTA-H-552, Pharmaceutical R&D, Costs, Risks and Rewards 67 (February 1993).

and cost of research, new drug development was estimated to cost on average somewhere in the vicinity of $500-600 million.[27]

As these average cost estimates evidence, new drug development is a lengthy process, and total drug development time has grown significantly. Average total drug development time has gone from 8.1 years as of 1960, to 11.6 years in the 1970s, to 14.2 years in the 1980s and 1990s. *See* Figure 1: Total Drug Development Time from Synthesis to Approval. Since 1980, the average number of clinical trials conducted prior to filing a new drug application (NDA) has more than doubled, and the number of patients in clinical trials has tripled.[28]

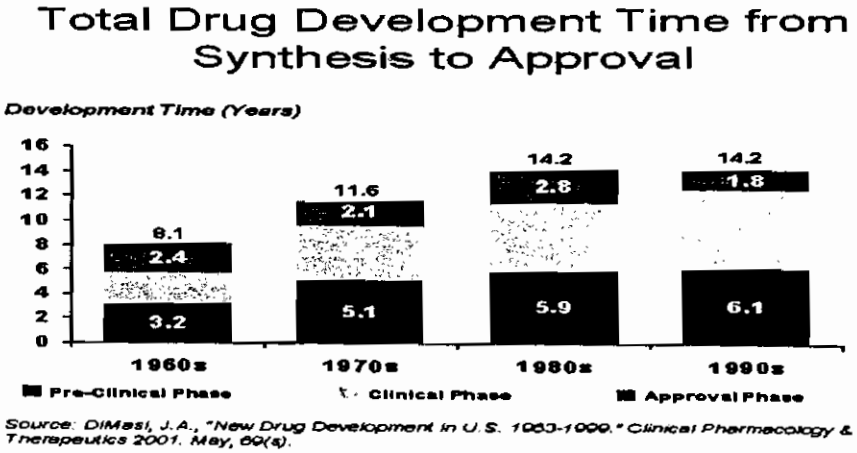

Figure 1

New drug development is also very risky. For every one drug that reaches market: (i) approximately 5,000-10,000 compounds are tested in pre-clinical trials; (ii) approximately 250 drugs are tested in pre-clinical animal trials; and (iii) approximately 5 are tested in full-scale, human clinical trials.[29] Companies generally allocate 30.6 percent of R&D expenditures to preclinical functions, and 25.6 percent of R&D costs to clinical trials (Phase I, II and III).[30] In addition, 8.8 percent of R&D costs are directed to Phase IV clinical trials, which occur after product approval by FDA.[31] *See* Figure 2 Compound Success Rates by Stages.

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[27] Boston Consulting Group, *Sustaining Innovation in U.S. Pharmaceuticals, Intellectual Property Protection and the Role of Patents* 13 (January 1996).

[28] PhRMA, 2001 Industry Profile, at VI; *see also id.* Figs. 3-3, 3-4 at 26, 27.

[29] PhRMA, 2002 Industry Profile, at 19, 20.

[30] *See id.* at table 5, at 79.

[31] *Id.*

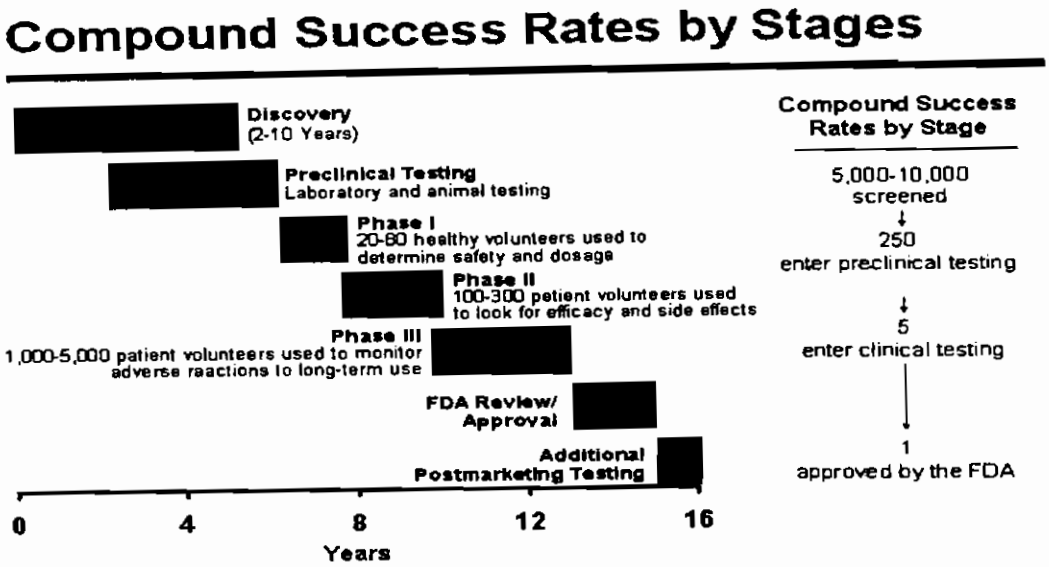

Figure 2

At the same time, average returns from marketing a new drug have dropped. A 1998 Congressional Budget Office report estimated that, for a variety of reasons, average returns to a pioneer from marketing a new drug had declined by approximately 12% since 1984.[32] Further, most marketed drugs are not profitable; "blockbusters" support most R&D.

According to a 1994 study of drugs introduced between 1980 and 1984, for every ten drugs that came to market, only three covered the average development costs.[33] The same study showed that the top 20% of products with the highest revenues generated 70% of the returns for the period 1980-1984.[34] Increasing development time and costs, and decreasing average returns suggest that even fewer new drugs now cover their development costs than did in 1980 to 1984.

Despite the great need for strong intellectual property protection, pioneer drug companies realize far less actual patent life than innovators in other industries. This is because of the lengthy drug development and approval process. On average, the effective patent life for drugs introduced from 1984-1995 that received patent term restoration, including such restoration, was

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[32] Congressional Budget Office, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry* (July 1998), *available at* http://www.cbo.gov (CBO 1998).

[33] *See* Grabowski & Vernon, *Returns to R&D on New Drug Introductions in the 1980s*, 13 J. of Health Econ. 383 (1994).

[34] *Id.*

only about 11 years.[35] Any action that further impairs patent protection for innovative pharmaceutical products could substantially reduce the number of new products that come to market.

D. The Strength of Intellectual Property Rights Protection Impacts Investment Decisions.

Direct investors demand a potential return on their investment commensurate with the high costs and risks of drug development. Accordingly, the pharmaceutical industry relies, in particular, upon patents to provide the opportunity to realize such commensurate returns.

The importance of intellectual property to investment decisions is borne out by comparisons of countries with and without strong intellectual property protection for pharmaceutical innovation. Pharmaceutical industry research in the United States, which accounts for nine out of ten prescription medicines on the market, would not be economically feasible without strong intellectual property protection.[36] In Mexico, R&D tripled after adoption of full intellectual property ("IP") protection in 1991.[37] Other countries that experienced R&D growth corresponding to strengthened IP are South Korea, Japan, and Italy.[38] Italy has experienced a four-fold increase in R&D investment since instituting strong IP protection in 1978.[39] Canada established a compulsory licensing system in 1969, weakened that system in 1987 and abandoned it in 1993. R&D expenditures by companies in Canada rose to $900 million in 1999 from $166 million in 1988.[40] In contrast, India, which stopped providing full patent protection in 1970, conducts only 0.001% of worldwide R&D.[41]

Trading activity in secondary markets also has reflected the importance of patent protection to investors. For example, an announcement in March 2000 by the Clinton administration urging the free availability of raw data on the human genome resulted in a number of biotechnology companies losing a substantial percentage of their market capitalization. The chief concern of investors—who sold shares in record numbers until the President's remarks

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[35] *See* S. Shulman, J. DiMasi & K. Kaitin, *Patent Term Restoration; The Impact of the Hatch-Waxman Act on New Drugs and Biologics Approval 1984-1995*, 2 J. Biolaw and Bus. 63, 66 (1999) (The Impact of the Hatch-Waxman Act).

[36] PhRMA, 2001 Industry Profile, at 92.

[37] *Id.* at 99.

[38] *Id.*

[39] *Id.* at 105, (citing Farmindustria Indicatori Farmaceutic i, 1994).

[40] Andrew Pollock, *Defensive Drug Industry; Fueling Clash over Patents*, N.Y. Times, April 20, 2001, at A.6.

[41] PhRMA, 2001 Industry Profile, at 100.

EXHIBIT 33

Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial

The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators*

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Summary

Background Rosiglitazone is a thiazolidinedione that reduces insulin resistance and might preserve insulin secretion. The aim of this study was to assess prospectively the drug's ability to prevent type 2 diabetes in individuals at high risk of developing the condition.

Methods 5269 adults aged 30 years or more with impaired fasting glucose or impaired glucose tolerance, or both, and no previous cardiovascular disease were recruited from 191 sites in 21 countries and randomly assigned to receive rosiglitazone (8 mg daily; n=2365) or placebo (2634) and followed for a median of 3 years. The primary outcome was a composite of incident diabetes or death. Analyses were done by intention to treat. This trial is registered at ClinicalTrials.gov, number NCT00095654.

Findings At the end of study, 59 individuals had dropped out from the rosiglitazone group and 46 from the placebo group. 306 (11·6%) individuals given rosiglitazone and 686 (26·0%) given placebo developed the composite primary outcome (hazard ratio 0·40, 95% CI 0·35–0·46; p<0·0001); 1330 (50·5%) individuals in the rosiglitazone group and 798 (30·3%) in the placebo group became normoglycaemic (1·71, 1·57–1·87; p<0·0001). Cardiovascular event rates were much the same in both groups, although 14 (0·5%) participants in the rosiglitazone group and two (0·1%) in the placebo group developed heart failure (p=0·01).

Interpretation Rosiglitazone at 8 mg daily for 3 years substantially reduces incident type 2 diabetes and increases the likelihood of regression to normoglycaemia in adults with impaired fasting glucose or impaired glucose tolerance, or both.

Introduction

Type 2 diabetes mellitus affects about 5% of adults worldwide; this prevalence is rising rapidly.[1] People with type 2 diabetes are at high risk of serious eye, kidney, nerve, and vascular complications, which cause substantial morbidity and mortality. People with impaired fasting glucose or impaired glucose tolerance are asymptomatic but are at high risk of future diabetes and vascular disease.[2]

Type 2 diabetes develops when pancreatic insulin secretion is insufficient to maintain normal glucose homoeostasis. Acarbose and metformin[3,4] reduce incident diabetes by 25–30%; lifestyle interventions that target diet and physical activity[5–7] reduce incident diabetes by more than 50%, but are difficult to sustain. Rosiglitazone is a thiazolidinedione that is approved for treatment of hyperglycaemia in patients with established type 2 diabetes. The drug activates peroxisome proliferator-activated gamma receptors, increases hepatic and peripheral insulin sensitivity,[8] preserves insulin secretion,[9] and might promote pancreatic β-cell health.[10,11] These properties, together with data from trials with troglitazone[12,13] (another thiazolidinedione that has been withdrawn because of hepatotoxicity), suggest that rosiglitazone could reduce the frequency of diabetes in high-risk individuals.

The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial was designed to assess prospectively whether rosiglitazone can reduce the frequency of diabetes in individuals with impaired glucose tolerance or impaired fasting glucose, or both.

Methods

Patients

A detailed description of the design of the DREAM trial has been published previously.[14] Briefly, 24592 people aged 30 years or more were assessed for eligibility with a 75 g oral glucose tolerance test between July, 2001, and August, 2003, at 191 sites in 21 countries. Inclusion criteria included either impaired fasting glucose (fasting plasma glucose concentration ≥6·1 mmol/L and <7·0 mmol/L and 2-h plasma glucose concentration <11·1 mmol/L during the oral glucose tolerance test) or impaired glucose tolerance (fasting plasma glucose concentration <7·0 mmol/L and 2-h plasma glucose concentration ≥7·8 mmol/L and <11·1 mmol/L). People with a history of diabetes (except gestational diabetes), cardiovascular disease (including heart failure and known low ejection fraction), or intolerance to either angiotensin-converting enzyme inhibitors or thiazolidinediones were excluded.

In 2003, the steering committee expanded the original eligibility criteria from impaired glucose tolerance to also include individuals with isolated impaired fasting glucose (fasting plasma glucose concentration ≥6·1 mmol/L and

<7·0 mmol/L and 2-h plasma glucose concentration <7·8 mmol/L) to broaden the generalisability of the study results.[14]

If deemed to be eligible, patients entered a 17-day single-blind placebo run-in period; participants who took at least 80% of run-in medication were subsequently enrolled for randomisation.

All participants were provided with advice by the local research staff about healthy diets and lifestyle habits to reduce diabetes. The study protocol and consent forms were reviewed and approved by the ethics committees of the participating centres, and all participants provided written informed consent.

Procedures

Eligible patients were randomly assigned (stratified by site) by a concealed, computerised telephone randomisation system to receive either rosiglitazone (4 mg once daily for the first 2 months and then 8 mg once daily) or matching placebo. The dose of 8 mg per day was chosen to achieve maximum ability to identify whether the drug prevents diabetes and to ensure that a negative study would not be attributed to an inadequate dose. Patients were concurrently randomly assigned to receive either ramipril (titrated to 15 mg once daily) or matching placebo with a 2×2 factorial design. Detailed results for the ramipril arm are described elsewhere.[15]

Participants attended visits 2 months and 6 months after randomisation and every 6 months thereafter. At all visits, the importance of healthy diet and lifestyle was emphasised, drugs were dispensed, and adherence was assessed and reinforced. A 75 g oral glucose tolerance test with local fasting and 2-h plasma glucose concentration measurements was done after 2 years and at final visit, and at other yearly visits local fasting plasma glucose and glycated haemoglobin concentrations were measured. If at any visit the fasting plasma glucose concentration was 7·0 mmol/L or greater or the 2-h plasma glucose concentration was 11·1 mmol/L or greater (ie, suggesting possible diabetes), an oral glucose tolerance test was scheduled within the next 3 months to either confirm or refute the diagnosis. If the second confirmatory oral glucose tolerance test was negative, participants then had yearly repeat measurements taken until the end of the study or until diabetes was diagnosed. If the fasting plasma glucose concentration was greater than 5·3 mmol/L and less than 7·0 mmol/L, and the glycated haemoglobin concentration was more than 93% of the upper limit of normal for the assay at any visit at which an oral glucose tolerance test was not done, such a test was scheduled for the next 6-month visit to test for possible diabetes as described above. If diabetes was diagnosed during the study and needed pharmacological therapy, the study drug was continued and antidiabetic agents other than a thiazolidinedione were allowed. Individuals who were not diagnosed with diabetes at the final active therapy visit entered a washout period to assess whether any diabetes-prevention properties of the study drug(s) persisted after discontinuation. They were switched to single-blind placebo and scheduled for a repeat oral glucose tolerance test after 2–3 months (results to be reported separately).

Participants had local measurements of alanine aminotransferase (ALT) concentrations every 2 months during the first year of therapy; subsequent ALT measurements were done at the discretion of the site physician. Waist and hip circumference and weight were measured and an electrocardiograph was done at study entry, after 2 years, and at the end of the study. Blood pressure was measured at 2 months, 6 months, 12 months, and yearly thereafter.

The composite primary outcome was incident diabetes or death from any cause during the active treatment period; death was included to account for the possibility that diabetes might develop at a different rate in individuals who die than in those who survive. Diabetes was diagnosed if (1) a locally measured fasting plasma glucose concentration of 7·0 mmol/L or greater or 2-h plasma glucose concentration of 11·1 mmol/L or greater during a 75 g oral glucose tolerance test was confirmed by a second test on a different day; (2) a single test was consistent with diabetes, no confirmatory test was done, and the masked adjudicator had no reason to reject the diagnosis; or (3) a physician diagnosed diabetes outside the study and the diagnosis was supported by the prescription of an antidiabetic agent and either a fasting plasma glucose concentration of 7·0 mmol/L or greater or any glucose concentration of 11·1 mmol/L or more. Diabetes status and date of diagnosis were established by masked adjudication of all relevant data.

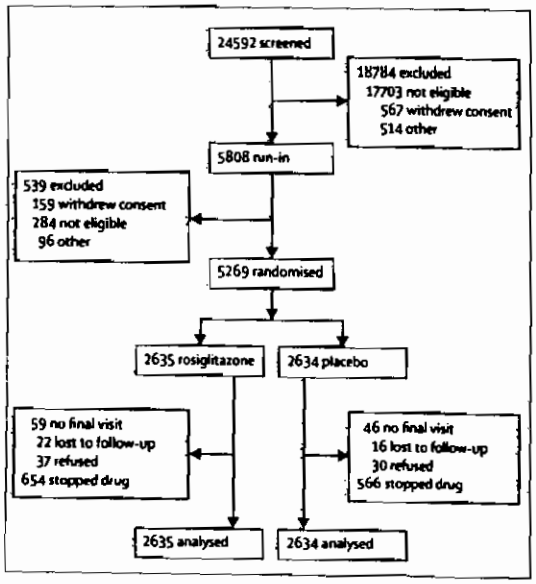

Figure 1: Trial profile
Data were censored at time of last follow-up for all participants.

	Rosiglitazone group (n=2635)	Placebo group (n=2634)
Mean age (years)	54·6 (10·9)	54·8 (10·9)
Women	1536 (58·3%)	1584 (60·1%)
Isolated IGT	1504 (57·1%)	1524 (57·9%)
Isolated IFG	369 (14·0%)	370 (14·1%)
Both IGT and IFG	762 (28·9%)*	740 (28·1%)*
Geographic distribution		
North America	1082 (41·1%)	1067 (40·5%)
South America	564 (21·4%)	572 (21·7%)
Europe	549 (20·8%)	555 (21·1%)
India	330 (12·5%)	332 (12·6%)
Australia	110 (4·2%)	108 (4·1%)
Medical history		
Gestational diabetes in women	139 (9·1%)	147 (9·3%)
History of hypertension	1159 (44·0%)	1132 (43·0%)
Current or former tobacco use	1157 (43·9%)	1193 (45·3%)
More than three alcoholic drinks per week	556 (21·1%)	503 (19·1%)
Sedentary	696 (26·4%)	717 (27·2%)
Drug use		
Aspirin or antiplatelet agent	378 (14·4%)	376 (14·3%)
Thiazide diuretics	246 (9·3%)	267 (10·1%)
Other diuretics or aldosterone antagonist	158 (6·0%)	145 (5·5%)
Angiotensin receptor blocker use	153 (5·8%)	133 (5·1%)
Beta-blocker	470 (17·8%)	442 (16·8%)
Calcium channel blockers	328 (12·5%)	349 (13·3%)
Alpha-blocker	43 (1·6%)	65 (2·5%)
Statin or fibrate	391 (14·8%)	389 (14·8%)
Weight loss drugs	16 (0·6%)	14 (0·5%)
Examination		
Weight (kg)	84·8 (19·0)	85·0 (18·9)
Body-mass index (kg/m²)	30·8 (5·6)	31·0 (5·6)
Waist/hip ratio (men; women)	0·96 (0·07); 0·86(0·07)	0·96 (0·07); 0·87 (0·09)
Waist (cm) (men; women)	101 (14); 96 (14)	102 (13); 96 (14)
Systolic blood pressure (mm Hg)	135·9 (17·9)	136·3 (18·8)
Diastolic blood pressure (mm Hg)	83·3 (10·6)	83·5 (10·9)
Investigations		
Mean fasting plasma glucose concentration (mmol/L)	5·8 (0·7)	5·8 (0·7)
Mean 2-h plasma glucose concentration (mmol/L)	8·7 (1·4)	8·7 (1·5)
Left ventricular hypertrophy on ECG	118 (4·5)	129 (4·9)

Data are mean (SD) or number (%). ECG=electrocardiograph. IFG=impaired fasting glucose (fasting plasma glucose concentration >6·1 mmol/L and <7 mmol/L and 2-h plasma glucose concentration <7·8 mmol/L). IGT=impaired glucose tolerance. *One individual in the rosiglitazone group and three in the placebo group who were randomised despite a fasting plasma glucose concentration >7 mmol/L were assumed to have developed diabetes on day 1.

Table 1: Baseline clinical and biochemical characteristics of participants

Secondary outcomes included: (1) regression to normal fasting and 2-h post-load glucose concentrations, defined as a fasting plasma glucose concentration of less than 6·1 mmol/L and a 2-h plasma glucose concentration of less than 7·8 mmol/L; (2) a composite of cardiovascular events (myocardial infarction, stroke, cardiovascular death, revascularisation procedures, heart failure, new angina with objective evidence of ischaemia, or ventricular arrhythmia needing resuscitation); (3) individual components of this cardiovascular composite; (4) renal events and a composite cardiorenal outcome; and (5) glucose concentrations. Clinical outcomes were assessed by masked adjudication by a committee in accordance with prespecified diagnostic criteria.

Statistical analysis

A sample size of at least 5000 individuals with impaired glucose tolerance or impaired fasting glucose was estimated on the basis of a predicted incidence of the primary outcome in the placebo group of 4·5% or greater per year, a mean follow-up exceeding 3 years, a type 1 error rate of 5%, 10% subadditivity between the two interventions, and 90% power to identify a risk reduction of 22% or greater. Interim results were reviewed every year by an independent trial monitoring committee whose role was to unblind and advise the principal investigators if there was evidence of clear benefit or harm. Statistical guidelines for benefit were a reduction in the primary outcome by 4 SD or more in the first half of the trial or 3 SD in the second half that was maintained during two consecutive analyses at least 3 months apart in the original cohort of participants with impaired glucose tolerance. Guidelines for harm included a sustained excess of cardiovascular events or death of 3 SD or more in the first half and 2 SD in the second half. The committee also took emerging information from other studies into account in their deliberations. In April, 2005, the committee informed the principal investigators that these criteria had been met for the subgroup of participants with impaired glucose tolerance in the rosiglitazone arm and unblinded them to that arm only. However, the principal investigators and the committee agreed that the study should continue because the average follow-up was short, the full 2-year data were not available, and the long-term safety data were inadequate. After its review of all the data in October, 2005, as well as new results from a large cardiovascular outcome trial of another thiazolidinedione,[16] the committee was sufficiently convinced that the study question had been clearly and robustly answered that it unblinded the principal investigators to the entire study results and recommended an accelerated but orderly close-out of the DREAM trial. This recommendation was agreed and final visits were started about 5 months earlier than originally anticipated.

All results were analysed at the Population Health Research Institute at McMaster University (Hamilton, Ontario, Canada), on the basis of intention to treat. Cox's proportional hazards models were used to estimate the effect of rosiglitazone on the hazard of the primary and other outcomes (stratified by ramipril allocation) and the significance of the effect. Interaction of the effect of rosiglitazone and ramipril on the primary outcome was assessed by including an interaction term in the Cox model. Individuals for whom diabetes status was unavailable at the end of the study were censored at the

time of their last glucose measurement. Kaplan-Meier curves for the primary and secondary outcome were constructed for rosiglitazone and placebo and compared with stratified log-rank tests. Statistical heterogeneity of treatment effects within key subgroups was also assessed. The effect of study drugs on glucose concentrations was assessed by calculating the median fasting and 2-h plasma glucose concentrations noted at every scheduled measurement time. Since an oral glucose tolerance test was not done after diabetes was diagnosed, and because any post-diabetes fasting plasma glucose measurements could have been lowered by diabetes management, a calculation of the median or mean values with every available measurement would have failed to accurately assess the effect of the interventions on glucose concentrations. Instead, median values were calculated by assigning people with diabetes the worst rank score for both the 2-h and fasting plasma glucose measurements,[17] and the groups were compared with a Wilcoxon rank-sum analysis. Analysis of variance (with adjustment for the baseline value) was used to assess differences between groups in the mean change in ALT after 1 year, and in systolic and diastolic blood pressure from the beginning to the end of the trial, and the slope of change of body-mass index, weight, waist-to-hip ratio, and waist and hip circumference during the course of the study. We used SAS version 9.1 (2002) for analyses.

This trial is registered at ClinicalTrials.gov, number NCT00095654.

Role of the funding source

All sponsors were represented on the steering committee and, together with the other members, provided feedback on study design, analysis, interpretation, and the final report. The sponsors had no role in the collection, storage, or analysis of the data, and were not involved in the decision to submit the data for publication. The Steering Committee decided to submit for publication, and the Hamilton Project office had full access to the data.

Results

5269 (21·4%) people with a mean age of 54·7 (SD 10·9) years (59·2% women) were randomly assigned to receive either placebo or rosiglitazone (figure 1). The baseline characteristics of the participants are shown in table 1. Of note, 3028 (57%) participants had isolated impaired glucose tolerance, 739 (14%) had isolated impaired fasting glucose, and 1502 (29%) had both.

Participants were followed for a median of 3·0 years (range 2·5–4·7). During the trial 992 (18·8%) individuals experienced the primary outcome: 63 (1·2%) people died and 938 (17·8%) people developed diabetes on the basis of either study-related glucose concentrations (n=786) or other criteria (152). Of the remaining participants, 3961 completed a final visit, 218 provided a verbal report of their diabetes status, and 98 did not respond. Vital status could not be ascertained in 105 (2·0%) people by the end of the trial; in these individuals, vital status was known for 2 years or more in 56 people, in 22 for 1–2 years, and in 27 for less than 1 year.

In surviving participants for whom adherence to study drug was recorded by the research staff (2604 individuals assigned rosiglitazone and 2600 assigned placebo), 1868 (71·7%) in the rosiglitazone group and 1952 (75·1%) in the placebo group were at least 80% adherent at the end of the study; two individuals in the rosiglitazone group and one in the placebo group were taking 4 mg daily; four receiving rosiglitazone and 16 receiving placebo were taking open-label rosiglitazone or

	Rosiglitazone group (n=2635)	Placebo group (n=2634)	HR (95% CI)	p
Composite primary outcome*	306 (11·6%)	686 (26·0%)	0·40 (0·35–0·46)	<0·0001
Diabetes	280 (10·6%)	658 (25·0%)	0·38 (0·33–0·44)	<0·0001
Diagnosed by FPG/OGTT	231 (8·8%)	555 (21·1%)	0·38 (0·33–0·44)	<0·0001
Physician diagnosed	49 (1·9%)	103 (3·9%)	0·47 (0·33–0·66)	<0·0001
Death	30 (1·1%)	33 (1·3%)	0·91 (0·55–1·49)	0·7
Regression (FPG <6·1 mmol/L)†	1330 (50·5%)	798 (30·3%)	1·71 (1·57–1·87)	<0·0001
Regression (FPG <5·6 mmol/L)†	1016 (38·6%)	540 (20·5%)	1·83 (1·65–2·04)	<0·0001
Cardiovascular events composite*	75 (2·9%)	55 (2·1%)	1·37 (0·97–1·94)	0·08
Myocardial infarction	15 (0·6%)	9 (0·3%)	1·66 (0·73–3·80)	0·2
Stroke	7 (0·3%)	5 (0·2%)	1·39 (0·44–4·40)	0·6
Cardiovascular death	12 (0·5%)	10 (0·4%)	1·20 (0·52–2·77)	0·7
Confirmed heart failure‡	14 (0·5%)	2 (0·1%)	7·03 (1·60–30·9)	0·01
New angina	24 (0·9%)	20 (0·8%)	1·20 (0·66–2·17)	0·5
Revascularisation	35 (1·3%)	27 (1·0%)	1·29 (0·78–2·14)	0·3
Myocardial infarction, stroke, or cardiovascular death	32 (1·2%)	23 (0·9%)	1·39 (0·81–2·37)	0·2

Data are number (%). *Rows are not mutually exclusive for components of the composite—if a participant had more than one component of the composite then they are counted in the relevant row. †Regression implies achieving a normal fasting glucose concentration (as defined in both rows) and 2-h plasma glucose level. ‡Defined as acute treatment with at least two of the following criteria: typical signs and symptoms, typical radiological evidence, use of diuretics, vasodilators, or inotropes. FPG=fasting plasma glucose. OGTT=oral glucose tolerance test.

Table 2: Primary and other outcomes

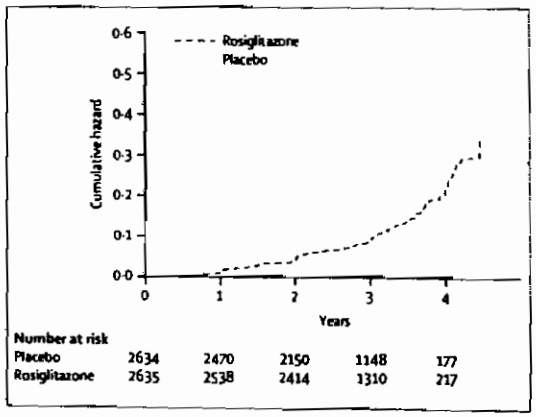

Figure 2: Time to occurrence of primary outcome

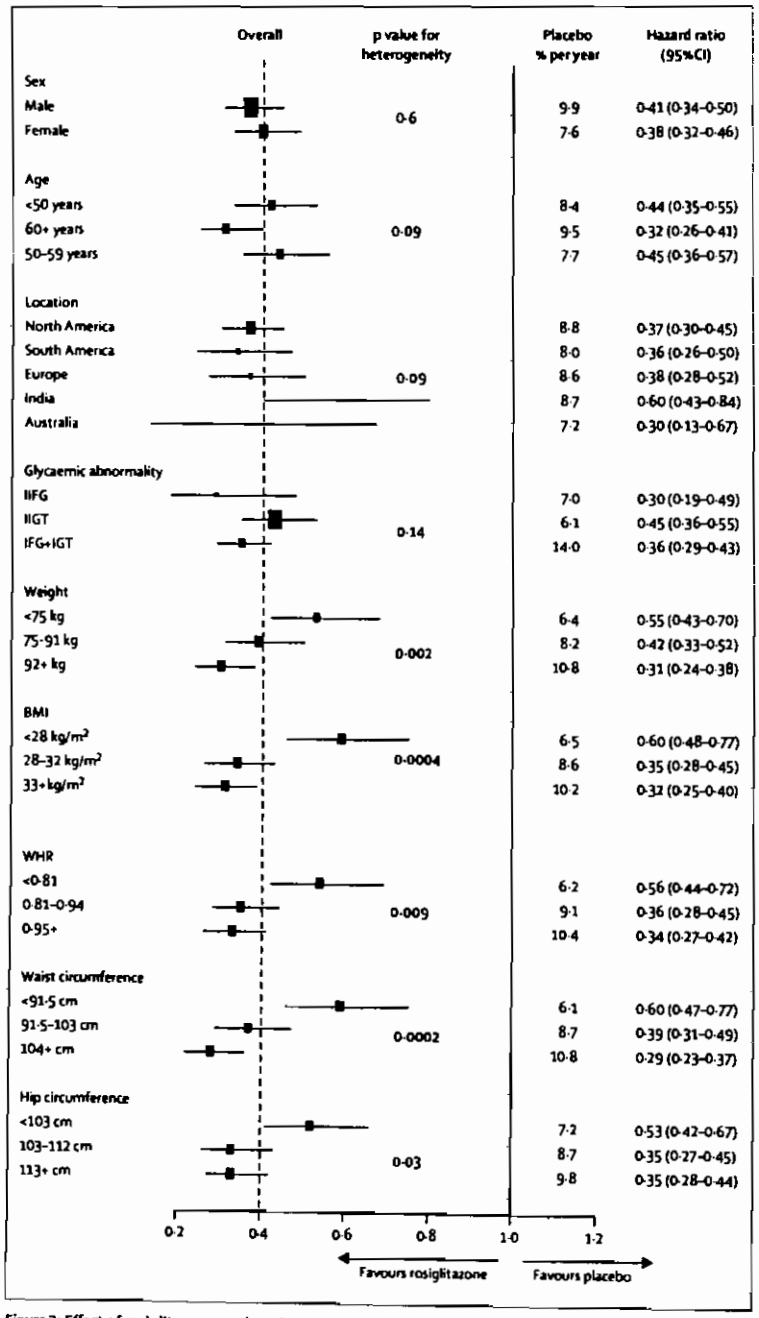

Figure 3: Effect of rosiglitazone on the primary outcome in key subgroups
BMI=body-mass index. IIFG=isolated impaired fasting glucose. IIGT=isolated impaired glucose tolerance. WHR=waist-to-hip ratio.

pioglitazone. 752 (28·5%) participants in the rosiglitazone group and 641 (24·3%) in the placebo group stopped taking their assigned treatment at any time; and 602 (23·6%) people assigned to receive rosiglitazone and 517 (20·2%) assigned to receive placebo were not taking the allocated drug at their last visit. The most common reasons for stopping rosiglitazone and placebo included participant refusal (503 [18·9%] in the rosiglitazone group and 439 [16·7%] in the placebo group); oedema (439 [4·8%] and 41 [1·6%]), physician's advice (50 [1·9%] and 39 [1·5%]), and weight gain (50 [1·9%] and 15 [0·6%]). One patient in the rosiglitazone group and three in the placebo group stopped because of hypoglycaemia.

There was no statistical evidence of an interaction between the rosiglitazone and ramipril arms of the DREAM study for the primary outcomes, secondary outcomes, or their components (interaction p>0·11 for all; data not shown). The primary outcome of diabetes or death was seen in significantly fewer individuals in the rosiglitazone group than in the placebo group (hazard ratio [HR] 0·40, 95% CI 0·35–0·46; p<0·0001; table 2). There was no difference in the number of deaths (0·91, 0·55–1·49; p=0·7) and a large difference in the frequency of diabetes (0·38, 0·33–0·44; p<0·0001) between the two groups (table 2). The event curves for the primary outcome diverged by the time of the first assessment (after 1 year of follow-up; figure 2).

Effects on the primary outcome were much the same irrespective of the glycaemic abnormality that was present at the time of randomisation. Thus, an HR for the primary outcome of 0·30 (0·19–0·49) was recorded in individuals with isolated impaired fasting glucose, of 0·45 (0·36–0·55) in those with isolated impaired glucose tolerance, and 0·36 (0·29–0·43) in those with combined impaired fasting glucose tolerance and impaired glucose tolerance (p value for heterogeneity 0·14; figure 3). When analysed on the basis of the fasting plasma glucose alone (ie, irrespective of whether or not impaired glucose tolerance was also present), participants with any impaired fasting glucose tolerance (ie, isolated impaired fasting glucose or impaired fasting glucose plus impaired glucose tolerance) had an HR of 0·35 (0·29–0·42) for the primary outcome. If impaired fasting glucose is defined as a fasting plasma glucose of 5·6 mmol/L to 6·9 mmol/L[18] the hazard for these participants (who in this study also had impaired glucose tolerance) was 0·41 (0·30–0·55).

The effect of rosiglitazone was much the same in all regions of the world, different ethnic groups, in both sexes, and across all ages (figure 3). Rosiglitazone was also effective irrespective of baseline weight or fat distribution, albeit to a different degree. Whereas increasing baseline weight or waist-to-hip ratio (ie, abdominal fat distribution) predicted a higher frequency of diabetes in individuals in the placebo group, this relation was not seen in those in the rosiglitazone group. Consequently the relative hazard reduction for the primary outcome increased from 40% in people whose body-mass index was less than 28 kg/m² to 68% in people whose body-mass index was greater than 32 kg/m² (p for heterogeneity 0·0004; figure 3).

A significantly larger number of participants receiving rosiglitazone regressed to normoglycaemia (defined as a 2-h plasma glucose concentration <7·8 mmol/L and fasting plasma glucose concentration <6·1 mmol/L) than did individuals receiving placebo (1330 individuals on rosiglitazone *vs* 798 on placebo; HR 1·71, 1·57–1·87; p<0·0001; table 2). The effect on regression was also evident when a more stringent definition of normal fasting plasma glucose concentration (<5·6 mmol/L) was used (1·83, 1·65–2·04; p<0·0001; table 2 and figure 4).

Both treatment groups had much the same frequency of the composite cardiovascular outcome and of every component of the composite except for heart failure (table 2). There were no cases of fatal heart failure; one person in the rosiglitazone group died of a myocardial infarction 1 month after a diagnosis of heart failure and one person died after a procedure done 2 years after stopping treatment with rosiglitazone. Increases in the risk of heart failure in the presence or absence of ramipril were much the same and were distributed throughout the follow-up period (data not shown). 174 (6·8%) of 2547 people in the rosiglitazone group reported peripheral oedema at the final visit versus 124 (4·9%) of 2554 people in the placebo group (p=0·003).

Figure 5 shows the effect of rosiglitazone on fasting and 2-h plasma glucose concentrations. The median fasting plasma glucose concentration was 0·5 mmol/L lower in the rosiglitazone group than in the placebo group (p<0·0001); the 2-h plasma glucose concentration was 1·6 mmol/L lower (p<0·0001). Mean systolic and diastolic blood pressure were 1·7 mm Hg and 1·4 mm Hg lower, respectively, in the rosiglitazone group than in the placebo group (p<0·0001). Furthermore, mean hepatic ALT concentrations during the first year of therapy were 4·2 U/L lower in patients treated with rosiglitazone than those in the placebo group (p<0·0001). All results are for the final visit apart from the ALT difference, which was at 1 year. Of note, there was no difference in the use of antihypertensive agents in the two groups during the trial. Finally, by the final visit mean bodyweight was increased by 2·2 kg more in the rosiglitazone group than in the placebo group (p<0·0001). This increase in bodyweight in the rosiglitazone group was associated with a lower waist-to-hip ratio (p<0·0001) because of an increase in hip circumference of 1·8 cm; there was no effect on waist circumference (figure 6).

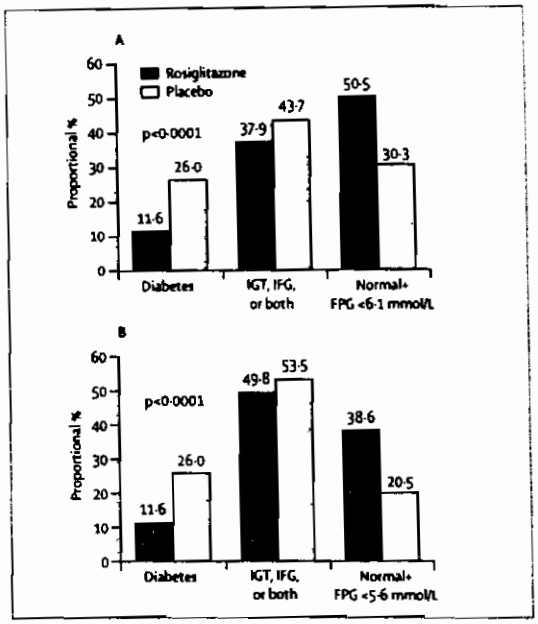

Figure 4: Proportion of participants who either developed diabetes, regressed to normal, or had impaired fasting glucose or impaired glucose tolerance, or both, at the last assessment
(A) FPG defined as concentration <6·1 mmol/L or (B) <5·6 mmol/L. The p value for the likelihood that the distribution across categories would have occurred by chance using both FPG cutoffs was <0·0001.

Discussion

This large, prospective, blinded international clinical trial shows that 8 mg of rosiglitazone daily, together with lifestyle recommendations, substantially reduces the risk of diabetes or death by 60% in individuals at high risk for diabetes. The absolute risk difference between treatment groups of 14·4% means that for every seven people with impaired fasting glucose or impaired glucose tolerance who are prescribed rosiglitazone for 3 years, one will be prevented from developing diabetes. Moreover, rosiglitazone significantly increased the likelihood of regression to normoglycaemia by about 70–80% compared with placebo. The reduction in diabetes reported here is of much the same magnitude as the reduction achieved with lifestyle approaches[4,5] and greater than the reductions reported previously with drugs such as metformin[4] or acarbose.[3] The effect on regression is

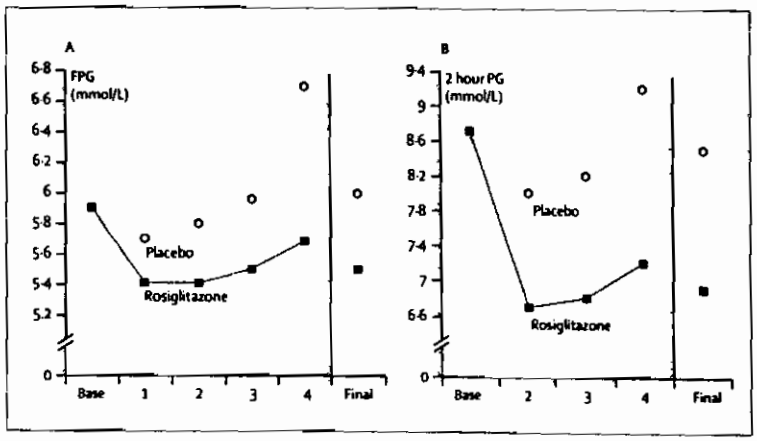

Figure 5: Effect of rosiglitazone on the point estimates of (A) fasting plasma glucose (FPG) and (B) 2-h plasma glucose (PG) concentrations

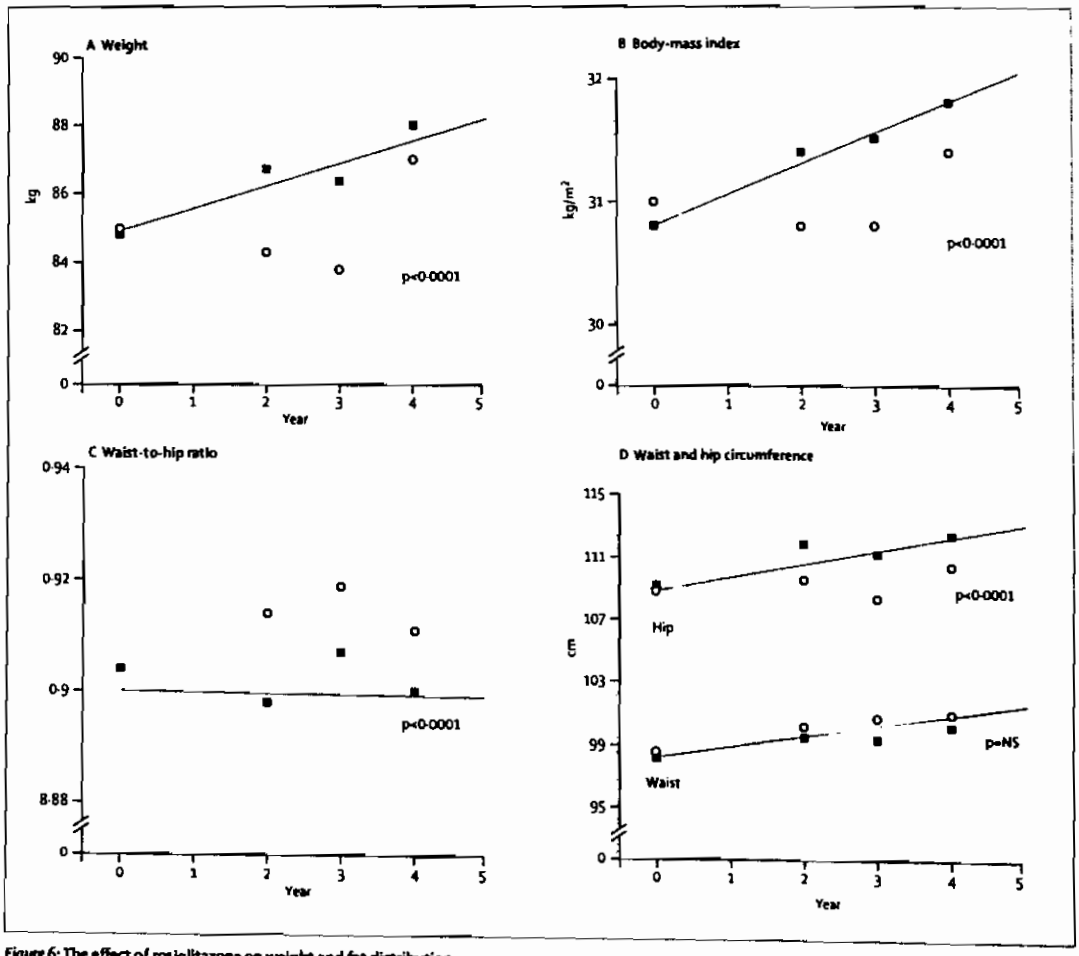

Figure 6: The effect of rosiglitazone on weight and fat distribution
Overall effect of rosiglitazone and placebo on the slope of (A) weight and (B) body-mass index, (C) waist-to-hip ratios in all participants, and (D) waist and hip separately. p values indicate the differences in slope and the markers indicate the mean values for rosiglitazone (square) and placebo (circle) at every time point. Weight, waist, and hip circumference were recorded at baseline, 2 years, and study end (3 or 4 years for most participants). NS=not significant.

much the same or larger than that of lifestyle approaches or acarbose, but larger than that with metformin, which did not promote more regression than placebo.[3,4] These results support findings from smaller clinical trials of troglitazone in people with either impaired glucose tolerance[12] or women with a history of gestational diabetes.[13]

A consistent reduction in the primary outcome was noted in people with impaired fasting glucose and those with impaired glucose tolerance, in men and women, in all participating regions of the world (consisting of many ethnic groups), in patients of all ages, and in participants of varying weight and fat distribution. Participants with a higher body-mass index or abdominal fat distribution who were allocated to receive rosiglitazone all had the same 3–4% per year incidence of the primary outcome, despite progressively higher rates in the corresponding control participants (data not shown); this finding accounts for the observation of higher risk reduction with higher baseline obesity (figure 3). Rosiglitazone therefore seems to reduce or eliminate the relation between increasing obesity and a higher risk of diabetes.

Several explanations could account for these findings. Rosiglitazone might simply reduce the raised glucose concentrations of dysglycaemic participants by increasing the effectiveness of endogenous insulin. If true, the effect on glucose concentrations should be largely eliminated upon withdrawal or washout of the drug; this will be formally tested during the post-trial washout period. Data from one previous troglitazone trial suggests that the benefits of a thiazolidinedione persist even after the drug is stopped;[19] this was not seen in another trial.[12] Alternatively, rosiglitazone could slow the fall in β-cell function with time by reducing the physiological demand

for basal as well as prandial insulin secretion (ie, through insulin sensitisation) or by a direct β-cell cytoprotective effect.[19] Another explanation is offered by the observation that the frequency of diabetes was lower in the rosiglitazone group than in the placebo group, despite a 2·2 kg increase in weight in the rosiglitazone group. The preferential deposition of fat in the hip versus the abdomen and the reduction in ALT concentrations noted during the first year of therapy suggests that this modest weight gain could have been due to fat accumulation in non-visceral compartments and an increase in subcutaneous adipocyte mass.[20] Such an effect could be accompanied by increased secretion of adiponectin and reduced levels of inflammatory cytokines, and is associated with less diabetes.[21,22]

Epidemiological studies and at least one clinical trial of people with cardiovascular disease suggest that thiazolidinediones might reduce cardiovascular events.[16,23] However, such a reduction was not the focus of this trial and the short observation period and low event rates (table 2) preclude drawing reliable conclusions with regard to the cardiovascular effects of rosiglitazone. Indeed, the DREAM trial explicitly excluded individuals with previously diagnosed cardiovascular disease because of clear evidence that ramipril reduced cardiovascular events in these individuals.[24] The effect of rosiglitazone on atherosclerosis, measured by sequential carotid ultrasounds in a subset of DREAM participants, will be reported elsewhere.

Rosiglitazone had no effect on the cardiovascular composite outcome, although blood pressure was significantly lower in those receiving the drug than those receiving placebo. However, as reported in thiazolidinedione studies done in people with diabetes,[25] there was a small excess in non-fatal congestive heart failure in those receiving rosiglitazone. These findings could be explained by the vascular and renal effects of the drug. Rosiglitazone-mediated vasodilation caused by both direct effects on blood vessels and increases in vascular insulin sensitivity accounts for the modest fall in blood pressure.[26] Sodium and water retention could occur as a result of a direct thiazolidinedione effect on the renal collecting duct and possibly in response to the modest fall in blood pressure.[25,27] The resulting fluid overload is probably responsible for congestive heart failure in susceptible individuals. The observation that the incidence of heart failure with a thiazolidinedione was about ten times lower in participants at low risk of cardiovascular events in the DREAM trial than in a cardiovascular prevention trial of participants at high risk[16] could be explained by a reduced susceptibility of lower risk people to heart failure. Nevertheless, since there were only 16 cases of heart failure, this estimate needs to be interpreted cautiously and further analyses of these data, together with data from other thiazolidinedione studies, are indicated to better identify people at risk.

More than 8% of adults worldwide have either impaired glucose tolerance or impaired fasting glucose.[1] Every year about 5–10% of these people will develop diabetes and acquire the disease burden related to its diagnosis, symptoms, need for surveillance for chronic consequences, and associated costs. They will also be at high risk for several chronic diseases. The results of this study suggest that the addition of rosiglitazone to basic lifestyle recommendations substantially reduces the risk of developing diabetes by about two-thirds, offering a novel preventive approach that could be as, or more, effective and sustained than previously reported lifestyle approaches alone.[4,5] Balancing both the benefits and risks suggests that for every 1000 people treated with rosiglitazone for 3 years, about 144 cases of diabetes will be prevented, with an excess of four to five cases of congestive heart failure. Finally, the observation that rosiglitazone increased the likelihood of regression to normoglycaemia by about 70–80% suggests that it is treating dysglycaemia as well as reducing the frequency of diabetes. Further work is needed to establish whether the beneficial metabolic effects seen with rosiglitazone will lead to a reduction in cardiovascular, renal, retinal, or other serious health consequences.[28]

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The members of the steering committee designed the trial, did the scientific review, and interpreted the data. The members of the writing committee wrote the manuscript and the people listed above by country contributed to recruitment and data collection. H C Gerstein and S Yusuf were co-principal investigators; R Holman was the European co-chair, and J Bosch was the project director.

Conflict of interest statement

H C Gerstein and S Yusuf have received honoraria for providing advice to, and speaking for, Sanofi-Aventis and GlaxoSmithKline. J Bosch has received honoraria for attending advisory committee meetings for Sanofi-Aventis. B Hoogwerf is a clinical investigator at GlaxoSmithKline and is involved in a phase III trial of a DDP-IV inhibitor. R R Holman has received honoraria from GlaxoSmithKline for attending advisory boards and speaking at symposia. M Laakso has been a consultant for Astra-Zeneca, GlaxoSmithKline, Merck Sharpe and Dohme, and Sanofi-Aventis, and has received speaker's fees from Bayer, Lilly, and Takeda, and travel or accommodation payments for consultancies and lectures. M Hanefeld has received honoraria for lectures from Sanofi-Aventis, Bayer, Takeda advisory board, Novo Nordisk, and GlaxoSmithKline. J Shaw has received honoraria from GlaxoSmithKline and Eli Lilly Australia for giving lectures and has received payment for being on the advisory board of Eli Lilly. B Zinman has received research support and honoraria for scientific advisory board and speaking from GlaxoSmithKline and honoraria for scientific advisory board and speaking from Sanofi-Aventis. The other members of the writing committee declare that they have no conflict of interest.

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EXHIBIT 34

Forbes.com

Health

Glaxo's Faustian Pill

Matthew Herper and Peter Kang 09.15.06, 6:30 PM ET

GlaxoSmithKline hoped to expand the market for its diabetes blockbuster Avandia with a big study of the drug as a preventative for diabetes. But a prominent drug safety advocate says he thinks the study, which was made public on Friday, shows the pill may put patients' hearts at risk.

In the 5,000-patient clinical trial, called DREAM, Avandia decreased by 62% the number of people with high blood sugar who developed diabetes. But the pill, which is the second biggest selling drug for London-based GlaxoSmithKline , also increased by 37% the rate of a collection of heart problems that included heart attacks and strokes.

The increase in heart problems missed a test for statistical significance, but it still raises concerns, says Steven Nissen, chairman of cardiology at the Cleveland Clinic.

"The strong trend toward increased cardiovascular events is very troubling," he says. He worries that a class of diabetes drugs known as PPAR-gamma pills has "consistently disappointed" in big studies. Nissen has been critical of safety issues with several drugs. He was one of the first to warn about the potential dangers of **Merck**'s Vioxx painkiller.

There had been widespread hope that in addition to treating diabetes, drugs like Avandia might actually decrease the risk of heart attacks and strokes by controlling blood sugar and lowering artery inflammation, a risk factor for heart attacks. However, it seems they may actually be causing heart problems. "The promise that the class would prevent cardiovascular events does not seem to be realized with current drugs," Nissen says.

Barry Goldstein, director of endocrinology at Thomas Jefferson University, disagrees. He says that the only real risk that turned up was the one for heart failure, and that it is difficult to draw comparisons between this study and those of newer medicines like **Bristol-Myers Squibb**'s Pargluva. "I don't see it as a worrisome signal," he says.

Nissen previously raised concerns about Pargluva, an experimental drug that was designed to regulate high blood sugar--a root cause of diabetes--in the same way as Avandia. Instead of decreasing the risk of heart problems, that pill, Nissen argued, increased them. Pargluva was never approved by the Food and Drug Administration.

Now that he has seen the data for Avandia, Nissen frets that increased heart problems may mar other drugs in the class. In the DREAM trial, patients on Avandia had 66% more heart attacks, 39% more strokes and 20% more died from cardiovascular causes. None of those values came anywhere close to statistical significance. But there was a statistically significant increase in the number of patients who developed heart failure, a deadly condition in which the heart muscle is weakened and the lungs can fill with water.

When all of these problems were taken together, they came close to being statistically significant. Even that is of concern, because the patients in the trial had a relatively low risk of developing heart attacks and had not yet developed diabetes. Patients who have full-blown diabetes are at much higher risk for heart attacks; a drug that controlled blood sugar but increased heart problems would not necessarily be a bargain.

The DREAM trial was designed to prove that giving Avandia to patients with high blood sugar could keep them from developing diabetes. It did just that. But the safety concerns may prevent Glaxo or rival Takeda--which has a similar drug called Actos--from capturing the huge market for patients with so-called "pre-diabetes."

In an editorial in *The Lancet*, where the trial results were reported, Jaakko Tuomilehto of the University of Helsinki and Nicholas Wareham of the MRC Epidemiology Unit in Cambridge, U.K., wrote that the cost and lack of long-term benefits are

likely to keep health care funders like governments and insurance companies from being willing to pay for Avandia as a preventative for diabetes. "Unfortunately," they write, "the greater benefits in higher risk individuals would have to be balanced against the likely increased risk of heart failure."

For weeks, analysts at some major investment banks have been skeptical about Glaxo's DREAM. On Sept. 7, research analysts at Bear Stearns wrote that even a positive result for the study might not be enough to convince the American Diabetes Association, which also wants to see a decrease in complications for diabetes before prescribing a preventative.

On Wednesday, Credit Suisse analyst Steve Plag also expressed doubt. "We believe that it is unlikely that DREAM will produce paradigm shifting data given the hurdle imposed by the current treatment of choice: diet and exercise," Plag wrote.

Still, the results are a scientific win because they show that it is possible to develop drugs that prevent diabetes. An entirely new class of treatments is racing to market in the form of Januvia and Galvus, experimental pills developed by Merck and Novartis, which work in a new way. The FDA is expected to approve or reject Januvia in mid-October and Galvus in November. It's possible that Merck and Novartis could find a way to walk through the door that Glaxo has already opened.

Investors took the announcement of the trial's results with a grain of salt. In a generally upbeat day on Wall Street, Glaxo's shares were virtually unchanged at $55.37. Had they been convinced that the drug's sales would take off, they could have been expected to bid the stock up.

GlaxoSmithKline did not immediately return a call for comment.

EXHIBIT 35

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Health Day

December 4, 2006

New Type 2 Diabetes Drug Delays Disease Progression
But side effects include cardiovascular risks, study finds

Amanda GardnerHealthDay Reporter

MONDAY, Dec. 4 (HealthDay News) -- One of a new class of diabetes drugs delayed the progression of type 2 diabetes along with the need to add additional medications.

But it's not clear how the findings will affect actual practice because diabetes drugs tend to involve a complicated constellation of benefits and side effects.

In particular, this drug, **Avandia** (rosiglitazone), resulted in blood sugar staying normal longer but carried with it various cardiovascular risks and is expensive.

"You have to take into consideration the potential benefit versus the potential risk," said Dr. Robert Rizza, past president of the American Diabetes Association and professor of medicine at the Mayo Clinic College of Medicine in Rochester, Minn.

The results of the trial are even less encouraging when taken in concert with a previous study that also found an excess of cardiovascular events.

"Because of the fact that adverse cardiovascular events went in the wrong direction in the [previous] trial and because they go in the wrong direction in this trial, I have concerns about the overall benefit of rosiglitazone in diabetic patients who are highly vulnerable to adverse cardiovascular outcomes, and this is not, in my view, a very favorable result," said Dr. Steven E. Nissen, interim chairman of the department of cardiovascular medicine at the Cleveland Clinic.

"Something is happening here which has pretty profound public health implications," added Nissen, who recently uncovered **cardiac** problems with muraglitazar, a not-yet-approved diabetes drug in the same class as **Avandia**, and published those findings in the Journal of the American Medical Association.

The new study appears in the Dec. 7 issue of the New England Journal of Medicine and is being released early to coincide with a presentation Monday at the World Diabetes Congress in Cape Town, South Africa.

More than 20 million people in the United States have type 2 diabetes, the most common form of the disease. People with this condition either don't produce enough insulin, or cells in the body don't utilize the hormone efficiently. Insulin is essential for transporting sugar from the blood to cells for energy. Keeping blood sugar levels normal or nearly normal is critical to reducing the risk of the long-term complications of diabetes such as **heart** disease, nerve damage, kidney damage, blindness and amputations.

According to an accompanying editorial in the journal, the approval of five new classes of anti-diabetes drugs in the past decade has left doctors unsure of which to use first or how to combine them with other drugs. In particular, it hasn't been clear how the class of drugs known as thiazolidenediones, which includes **Avandia** and muraglitazar, compare with other glucose-lowering medications. These drugs work by sensitizing muscle, liver and fat tissue to insulin.

This study compared 4,360 newly diagnosed type 2 diabetes patients receiving either **Avandia** (rosiglitazone, a thiazoidinedione made by GlaxoSmithKline); glyburide (Micronase); or metformin (Glucophage). Prior to the study, participants had not taken any medications for diabetes.

The trial was sponsored by Glaxo, and study lead author Dr. Steven Kahn disclosed having served as a consultant and speaker for the company.

Avandia delayed the need for additional drugs by 60 months, compared with 45 months for Glucophage and 33 months for Micronase.

Participants taking **Avandia** had more weight gain and edema while participants on Micronase had a lower risk of cardiovascular events. One unexpected finding was that women taking **Avandia** had more fractures, primarily in the hands and feet.

A surprisingly high proportion of participants dropped out of the study, the editorial pointed out.

And not only did **Avandia** have cardiovascular effects, it did so even though patients in this group were taking more of the cholesterol-lowering drugs known as statins because the drug appeared to raise their LDL ("bad") cholesterol, Nissen said.

Avandia seems clearly superior to Micronase, but the distinction between **Avandia** and Glucophage is less clear.

"In my opinion, the use of [Micronase] for any reason other than cost is going to become harder to justify," said Kahn, associate chief of staff for research at Veterans Affairs Puget Sound Health Care System and professor of medicine at the University of Washington, Seattle. "On the other hand, when you compare [Glucophage] and [**Avandia**], this is where it starts to become a little grayer... A lot more has to be done in terms of human investigation."

Overall, it's still not clear how physicians should treat patients.

"We're being inundated by medications, and we're being overwhelmed by patients who are not controlled by either one or even two medications. So, we're really talking about a condition that's going to be treated with multiple medications," said Dr. Stuart Weiss, clinical assistant professor of medicine at New York University School of Medicine. "The only thing that we can say is that combination therapy might be the best way to go from the beginning, and this study doesn't even address that."

More information

For more about type 2 diabetes, visit the National Diabetes Information Clearinghouse.

---- INDEX REFERENCES ----

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